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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: POLYAMINE DERIVATIVES OF 1-AMINOINDAN			
(57) Abstract			
<p>A compound of general formula (I), wherein n is 1 or 2; R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, hydroxy, substituted or unsubstituted C<sub>1-4</sub> alkyl, substituted or unsubstituted C<sub>1-4</sub> alkoxy or halogeno; R<sub>5</sub> is hydrogen, substituted or unsubstituted C<sub>1-4</sub> alkyl, amino or NR<sub>6</sub>R<sub>7</sub>; R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> wherein m is from 0-5, y is from 0-5 and each x is independently from 1-5 and R<sub>11</sub> is hydrogen or C(NH)NH<sub>2</sub>; provided that when R<sub>3</sub> and R<sub>4</sub> are both hydrogen, R<sub>5</sub> is amino or NR<sub>6</sub>R<sub>7</sub>; pharmaceutically acceptable salts and optically active isomers thereof.</p>			
<p style="text-align: right;">(I)</p>			

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POLYAMINE DERIVATIVES OF 1-AMINOINDAN

5 Throughout this application, various references are referred to. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

10

Background of the Invention

15 The present invention relates to novel polyamines, compositions containing them and their use in the treatment of neurotrauma such as stroke.

20 Polyamines as a class of compounds have been reported to possess a wide range of activities both within and external to the central nervous system. Such activities include modulation of postsynaptic receptors, such as 25 nicotinic, glutamic and N-methyl-D-aspartate receptors, modulation of calcium regulatory processes as well as antiplatelet, antiinflammatory and anticoagulant activity.

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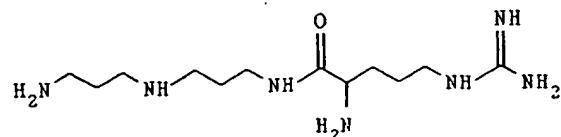
30 Various polyamine containing molecules have been synthesized and screened in a variety of animal models of disorders of the central nervous system. Many of these compounds have been based on toxins extracted from spiders such as A. aperta and Argiope labata and the wasp P. triangulum. These compounds comprise a long poly(aminoalkane) chain linked to an aromatic or heterocyclic group through a carbonyl group.

35 Guanidine derivatives of polyamines, e.g. SFTX-33 have been reported as voltage-sensitive calcium channel blockers and EAA antagonists capable of binding at the PCP site on the NMDA receptor. U.S. Patent No. 4,906,779 (Oregon 1990). Spergualine and

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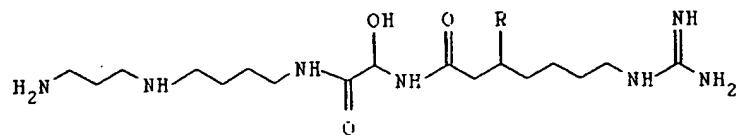
deoxypergualine has been reported (R.J. Bergeron, J.S. McManis, *J. Org. Chem.*, 52, 1700 (1987); *Drug Fut.*, 16, 165 (1991)) to possess immunosuppressant activity and beneficial effect in the treatment of Multiple Sclerosis.

10



sFTX-33

15



spergualine (R=OH)  
deoxyspergualine (R=H)

20

Gilad G et al. (*Life Sci.* (1989) 44 1963-1969 and *Exp. Neurol.* (1991) 111 349-355) have described activity of the polyamines spermine, spermidine and putrescine in protecting against ischemia induced nerve cell death in gerbils.

30

Disadvantages associated with using the simple polyamines described in Gilad G et al. relate to transport through biological membranes and various toxic side effects that would hinder these compounds from proceeding to clinical use.

35

Accordingly, the present invention provides derivatives of spermine, spermidine, and putrescine and guanidine

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derivatives thereof that retain the activity of the polyamine but display fewer undesirable side effects.

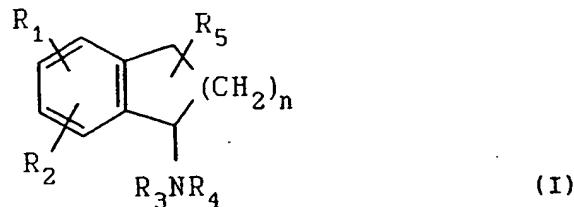
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Summary of the Invention

This invention provides compounds of general formula I

5

10



wherein n is 1 or 2;

R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, hydroxy, substituted or unsubstituted C<sub>1-4</sub> alkyl, substituted or unsubstituted C<sub>1-4</sub> alkoxy or halogeno;

15 R<sub>5</sub> is hydrogen, substituted or unsubstituted C<sub>1-4</sub> alkyl, amino or NR<sub>6</sub>R<sub>7</sub>;

R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> wherein m is from 0-5, y is from 0-5 and each x is independently from 1-5, R<sub>11</sub> is hydrogen or C(NH)NH<sub>2</sub>;

20 provided that when R<sub>3</sub> and R<sub>4</sub> are both hydrogen, R<sub>5</sub> is amino or NR<sub>6</sub>R<sub>7</sub>; pharmaceutically acceptable salts and optically active isomers thereof.

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Description of Figures

Figure 1A: Scheme I - Schematic of chemical synthesis Examples 1-5.  
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Figure 1B: Scheme I continued.

Figure 2: Scheme II - Schematic of chemical synthesis Example 6.

10 Figure 3: Scheme III - Schematic of chemical synthesis of Example 7.

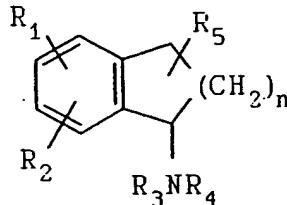
Figure 4: Schematic of chemical synthesis of Example 8.

Detailed Description of the Invention

This invention provides compounds of general formula I

5

10



(I)

wherein n is 1 or 2;  
 R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, hydroxy, substituted or unsubstituted C<sub>1-4</sub> alkyl, substituted or unsubstituted C<sub>1-4</sub> alkoxy or halogeno;  
 15 R<sub>5</sub> is hydrogen, substituted or unsubstituted C<sub>1-4</sub> alkyl, amino or NR<sub>6</sub>R<sub>7</sub>;  
 R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> wherein m is from 0-5, y is from  
 20 0-5 and each x is independently from 1-5, R<sub>11</sub> is hydrogen or C(NH)NH<sub>2</sub>;  
 provided that when R<sub>3</sub> and R<sub>4</sub> are both hydrogen, R<sub>5</sub> is amino or NR<sub>6</sub>R<sub>7</sub>; pharmaceutically acceptable salts and optically active isomers thereof.

25 Within general formula I it is generally preferred that n is 1, that is the compounds are derivatives of 1-aminoindan. It is further preferred that R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, hydroxy or halogeno, most 30 preferably R<sub>1</sub> and R<sub>2</sub> are both hydrogen. In a more specific embodiment R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen.

In one embodiment of the invention one of R<sub>3</sub> and R<sub>4</sub> is hydrogen and the other is of the formula (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub>. In such an embodiment it is preferable 35 that R<sub>11</sub> is hydrogen, m is 3 or 4, y is 0,1 or 2 and x where appropriate is 3 or 4. When y is more than 1 it is

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preferable that each x is 3 or 4.

Alternatively, one of R<sub>3</sub> and R<sub>4</sub> are hydrogen and the other is of the formula (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NH-C(NH)NH<sub>2</sub>, 5 i.e. R<sub>11</sub> is C(NH)NH<sub>2</sub>, m, y and x being as defined above.

In an alternative embodiment both R<sub>3</sub> and R<sub>4</sub> are of the formula (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub>. In this alternative embodiment it is preferable that m is 3 or 4 and y is 0, 10 1 or 2 more preferably 0. In a specific embodiment, R<sub>11</sub> is H.

In a further alternative embodiment of the invention, both R<sub>3</sub> and R<sub>4</sub> are hydrogen and R<sub>5</sub> is amino or NR<sub>6</sub>R<sub>7</sub>, 15 wherein R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or of the formula (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> with m, x, y and R<sub>11</sub> taking the preferences described above. Preferably R<sub>5</sub> is amino or N(CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> with m being 3 or 4, y being 0 and R<sub>11</sub>, hydrogen.

20 The compounds of formula I are aminoindan or aminotetralin analogs of spermine, spermidine, and putrescine and guanidine derivatives thereof and isomers of these polyamines. Many of the compounds of general 25 formula I are optically active. The present invention further relates to the purified optically active isomers.

30 In such embodiments when R<sub>5</sub> is not hydrogen, the R<sub>5</sub> group may exist in either the cis or trans configuration with respect to the group NR<sub>3</sub>R<sub>4</sub>. In such circumstances it is preferable that R<sub>5</sub> and the group NR<sub>3</sub>R<sub>4</sub> are in the cis configuration.

35 In all the above embodiments, the ring carbon to which the NR<sub>3</sub>R<sub>4</sub> group is bound may be in the "R" or "S" configuration, preferably it is in the "R"

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configuration.

Specific embodiments of the compound of general formula I include the following: N-(3-aminopropyl)-1-aminoindan;

5       N-(4-aminopropyl)-1-aminoindan;

N,N-di(4-amino-n-butyl)-1-aminoindan;

(R)-N,N-di(4-amino-n-butyl)-1-aminoindan;

(S)-N,N-di(4-amino-n-butyl)-1-aminoindan;

N-(4-amino-n-butyl)-N-(3-amino-n-propyl)-1-aminoindan;

10      N,N-di(4-amino-n-butyl)-1-amino-1,2,3,4-tetrahydronaphthalene;

N-[N-(4-aminobutyl)-3-aminopropyl]-1-aminoindan;

N-[N-(3-aminopropyl)-4-aminobutyl]-1-aminoindan;

N-{[N-(3-aminopropyl)-4-aminobutyl]-N'-3-aminopropyl}-15      1-aminoindan;

N-{[N-(4-aminobutyl)-3-aminopropyl]-N'-4-aminobutyl}-1-aminoindan;

cis N,N'-diacetyl-1,3-diaminoindan;

trans N,N'-diacetyl-1,3-diaminoindan;

20      cis 1,3-diaminoindan;

trans 1,3-diaminoindan;

N-(4-aminobutyl)-1,3-diaminoindan;

N,N'-di(4-aminobutyl)-1,3-diaminoindan;

N-(3-aminopropyl)-N-[N-(3-aminopropyl)-4-aminobutyl]-1-

25      aminoindan;

N,N-di(4-guanidinobutyl)-1-aminoindan;

N-(4-guanidinobutyl)-1-aminoindan, and pharmaceutically acceptable salts thereof.

30      The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of at least one of the above-listed compounds and a pharmaceutically acceptable carrier.

35      This invention provides for the pharmaceutical composition wherein the pharmaceutically acceptable carrier is a solid and the pharmaceutical composition is

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a tablet. In an embodiment the therapeutically effective amount is from about 1 mg to about 1000 mg. In a more specific embodiment the therapeutically effective amount is from about 10 mg to about 100 mg.

5

In another embodiment of the pharmaceutical composition the pharmaceutically acceptable carrier is a liquid and the pharmaceutical composition is an injectable solution. In a specific embodiment the therapeutically effective amount is from about 1 mg/ml to about 1000 mg/ml. In a more specific embodiment the therapeutically effective amount is from about 10 mg/ml to about 100 mg/ml.

10

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In an embodiment of the pharmaceutical composition the carrier is a gel and the pharmaceutical composition is a suppository.

20

25

This invention further provides a method for treating acute neurological traumatic disorder or neurotrauma in a subject comprising administering to the subject a therapeutically effective amount of a compound of the formula I or pharmaceutically acceptable salt thereof, effective to treat the acute neurological traumatic disorder or neurotrauma on the subject.

30

The subject can be any vertebrate, but is preferably a mammal, for example a cow, goat, sheep, horse, dog, monkey, ape, rabbit, rat or mouse. Most preferably the mammalian subject is a human.

35

The subject invention further provides a method of treating a subject afflicted with a neurodegenerative disease which comprises administering to the subject an amount of a compound of general formula I or the pharmaceutically acceptable salt thereof of the subject invention effective to treat the neurodegenerative

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disease in the subject.

The subject invention further provides a method of  
treating a subject afflicted with a neurotoxic injury  
5 which comprises administering to the subject an amount  
of a compound of general formula I or the  
pharmaceutically acceptable salt thereof of the subject  
invention effective to treat the neurotoxic  
injury in the subject.

10 The subject invention further provides a method of  
treating a subject afflicted with brain ischemia which  
comprises administering to the subject an amount of a  
compound of general formula I or the pharmaceutically  
15 acceptable salt thereof of the subject invention  
effective to treat brain ischemia in the subject.

20 The subject invention further provides a method of  
treating a subject afflicted with a head trauma injury  
which comprises administering to the subject an amount  
of a compound of general formula I or the  
pharmaceutically acceptable salt thereof of the subject  
invention effective to treat the head trauma injury in  
the subject.

25 The subject invention further provides a method of  
treating a subject afflicted with a spinal trauma injury  
which comprises administering to the subject an amount  
of a compound of general formula I or the  
30 pharmaceutically acceptable salt thereof of the subject  
invention effective to treat the spinal trauma injury in  
the subject.

35 The subject invention further provides a method of  
preventing nerve damage in a subject which comprises  
administering to the subject an amount of general  
formula I or the pharmaceutically acceptable salt

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thereof of the subject invention effective to prevent nerve damage in the subject.

5       The terms acute neurological traumatic disorder or neurotrauma are used herein to refer to, and include clinical indications such as strokes, acute cranial injury.

10      The compounds of the present invention are also of use as immunosuppressants, as anti-neoplastic agents, anti-psoratic agents and in the treatment of epilepsy, Alzheimer's Disease, multiple sclerosis, as insecticides and pesticides against endo- and ectoparasites.

15      The compound of general formula I, its salts and optically active isomers can be administered using techniques well known in the art. For example, the compound may be administered orally, rectally, parenterally, intravencusly, or intramuscularly.

20      To aid the discussion of the preparation of the compounds of the present invention it is convenient to classify them as follows:

25      1) Diamines (e.g. derivatives of putrescine or analogues with a different number of methylene groups in the alkyl chain;

30      2) Triamines (e.g. derivatives of spermidine or analogues with differing numbers of methylene groups in the alkyl chain;

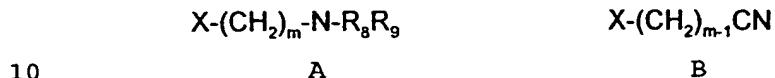
35      3) Tetramines (e.g. derivatives of spermine or analogues with differing numbers of methylene groups in the alkyl chain;

4) Compounds with five or more amino groups which are

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not direct derivatives of natural polyamines.

With reference to the schemes diagrammed in Figures 1 and 2, the compounds of the present invention may be prepared from the parent 1-aminoindan or 1-aminotetralin by reaction with a compound of the formula A or B.



wherein m is defined as previously and X is a suitable leaving group (such as halide or sulfonate ester) to enable N-alkylation by A or B; and one or both of R<sub>8</sub> and R<sub>9</sub> are suitable amino protecting groups such as t-butyloxycarboxy (BOC) or together are phthaloyl. Alternatively the terminal nitrile group of compound B fulfills the same role as an amine protecting group.

20 The reaction between the 1-aminoindan or 1-  
aminotetralin can be controlled to give predominantly  
either diamines or symmetrical triamines or a mixture  
of the two which may be separated into pure compounds  
by methods known to those skilled in the art  
25 (chromatography, crystallization, etc.). The desired  
diamines or symmetrical triamines may be isolated by  
removing the protecting groups under the appropriate  
conditions. For example if R<sub>8</sub> in IA is BOC, treatment  
with hydrogen chloride in ether. If R<sub>8</sub>R<sub>9</sub> in IA is  
30 phthaloyl, treatment with hydrazine. If the  
protecting group is nitrile in IB it is reduced with  
lithium aluminum hydride (LAH). In general the  
diamine is isolated as the salt of a suitable acid  
(e.g. hydrochloric, sulfuric, methansulfonic, etc.).  
35

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second alternative compound of the formula A or B with the partially protected diamine (I). The terminal protecting groups may then be removed according to methods described immediately above.

5

Other unsymmetrical triamines may be prepared by reacting a second alternative compound of the formula A or B and the suitably protected diamine (III) which is prepared from partially protected diamine (I) by introducing a second protecting group on the secondary amine to give fully protected diamine (II). The second protecting group ( $R_{10}$ ) is chosen so that the terminal primary amine protecting group ( $R_8R_9$  or nitrile) may be selectively converted to a free amine in its presence. For example, if  $R_8R_9$  is phthaloyl,  $R_{10}$  may be BOC. In the case where  $R_8R_9$  of the fully protected diamine (IIA) is phthaloyl, it may be selectively removed by treatment with hydrazine to give a compound of formula (III). In the case where the fully protected diamine (IIB) has a nitrile group, it may be selectively reduced with LAH likewise to give a compound of formula (III). In either case, the resulting compound of formula (III) may be reacted with a compound of formula A or B as described above to give a partially protected triamine of formula (IV). The desired triamine may be isolated as a suitable salt by removal of the protecting groups under the appropriate conditions as described above and subsequent reaction with a suitable acid.

30 Alternatively, the partially protected triamine (IV) may be converted to a tetramine by repeating the process described above (full protection to (V) and selective deprotection to (VI)). The resulting partially protected tetramine (VII) may be fully deprotected to isolate the tetramine or the protection/partial deprotection may be repeated to a

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pentamine, or higher homologue.

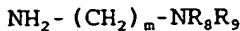
In a further embodiment of the invention the indan or tetralin skeleton forms an integral part of the 5 polyamine structure. In this case the diamine compound may be 1,3-diaminoindan (or 1,3-diaminotetralin) or 1,4-diaminotetralin. Each analogue may be isolated as the cis or trans isomer. They may be prepared from the corresponding diketone 10 by reaction with hydroxylamine hydrochloride followed by reduction (preferably using sodium in alcohol (preferably ethanol or isopropanol) or catalytic hydrogenation, preferably with palladium on carbon. The resulting cis/trans mixture of diamines may be 15 resolved by any convenient means, preferably by conversion to the diacetyl amide and resolution by crystallization and/or chromatography. The isomerically pure diacetates may be hydrolyzed to the desired diamines under acidic conditions (preferably 20 aqueous hydrochloric acid).

In analogy to the procedures described above, these 25 diamines may be converted to triamines and tetramines by reaction with compounds of the formula A or B (preferably B). In general, such a reaction results in a mixture of triamine (XI) and tetramine (XII) which may be separated by any convenient means, preferably by chromatography after converting them to the fully protected analogues (XIII) and (XIV), R<sub>10</sub> 30 preferably is BOC. After resolution, the protecting groups are removed from the resulting pure compounds (XIII) and (XIV) preferably using LAH for the nitrile and hydrogen chloride in ether for the BOC. The desired compounds (XV) are thus isolated as a suitable 35 salt (hydrochloride, sulfuric acid, methanesulfonic acid etc) as relatively pure cis or trans isomers.

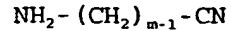
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In a further embodiment of the invention, tetramines of the formula XVI can alternatively be prepared directly from the indan or tetralin diketone by reaction with a mono-protected diamine of formula C or

5 D



C



D

10 where m, R<sub>8</sub> and R<sub>9</sub> are all as defined previously, to give the corresponding imine (XVII) which may be reduced (preferably with sodium borohydride or by catalytic hydrogenation) followed by deprotection under conditions appropriate for the protecting group, preferably acid hydrolysis for the case where R<sub>8</sub> is BOC. In this case XVI is isolated as a mixture of cis and trans isomers.

20 Unsymmetrical tetramines, e.g. compound 3069, may be prepared from the partially protected triamine (XXII) by introducing an appropriately protected aminoalkyl group, followed by removal of the protecting groups.

25 The triamine XXII may be prepared from 1-aminoindan by stepwise alkylations, starting with a protected aminoalkyl group, followed by a cyanoalkyl moiety. The nitrile group may subsequently be reduced with LAH and protected to give XXII.

30 The guanidine derivatives (compounds 3042, 3043) may be prepared by reacting the corresponding diamines or triamines with a guanylating agent e.g. N,N-di-tert-butoxycarbonylthiourea, (Iwanowicz E et al. Synthetic Communications (1993) 23, 1443), in a polar aprotic medium e.g. DMF, in the presence of an organic base e.g. triethylamine, optionally in the presence of a metal halide e.g. copper chloride or mercuric

35

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chlorides, and finally removing the Boc protecting groups by known methods, such as gaseous HCl in organic solvents.

5 This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully  
10 in the claims which follow thereafter.

Experimental Details

Many of the specific compounds are identified by a  
15 four-digit number from 2709 to 2732 and 3042, 3043 and 3069. Structures and names of these compounds may be found immediately following Chemical Synthesis Example 8.

20 CHEMICAL SYNTHESIS EXAMPLES

EXAMPLE 1

Preparation of phthalimidoalkylaminoindans [6].

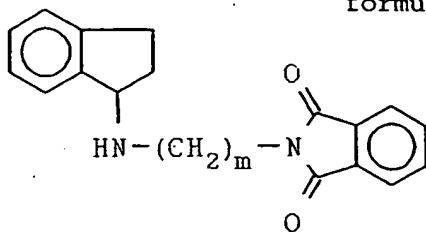
25 A mixture of 0.14mol of aminoindan or IA, 0.14mol of bromoalkylphthalimide and 0.14 mol of K<sub>2</sub>CO<sub>3</sub>, in 180ml of MeCN was stirred at bath temperature 50°C for 8 hours. After cooling and filtration, the mother liquor was  
30 evaporated. The residue was chromatographed on Keiselgel. Eluent: hexane-ethyl acetate 1:1.

In this way the following compounds were prepared;

-17-

Compounds of the  
formula 1A

5



m=3, 56% yield.

10

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.85-7.63 (m, 4H,), 7.31-7.10 (m, 4H,), 4.2 (t, J=6.5Hz, 1H), 3.83-3.81 (m, 2H), 3.01-2.95 (m, 1H), 2.83-2.71 (m, 3H), 2.40-2.33 (m, 1H), 1.94-1.56 (m, 3H).

15

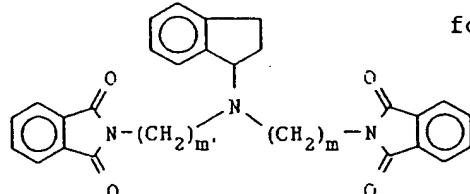
m=4, 54% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.88-7.65 (m, 4H,), 7.32-7.15 (m, 4H,), 4.22 (t, y=6.5Hz, 1H), 3.79-3.68 (m, 2H), 3.02-2.95 (m, 1H), 2.85-2.73 (m, 3H), 2.43-2.34 (m, 1H), 1.87-1.22 (m, 5H),

and

25

Compounds of  
formula 1A'



30

m=m'=4, 8% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.88-7.68 (m, 8H), 7.32-7.11 (m, 4H), 4.46 (t, y=7.5Hz, 1H), 3.68-3.62 (m, 4H), 2.90-2.65 (m, 2H), 2.48-2.33 (m, 4H), 2.10-1.85 (m, 2H), 1.80-1.45 (m, 8H),

35

m=3, m'=4, 26% yield using a 100% excess of bromopropylphthalimide.

-18-

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.83-7.66 (m, 8H), 7.33-7.10 (m, 4H), 4.50 (t,  $\gamma=7.5\text{Hz}$ , 1H), 3.86-3.65 (m, 4H), 2.90-2.75 (m, 2H), 2.51-2.40 (m, 4H), 2.10-1.51 (m, 8H),

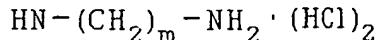
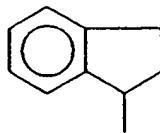
5      EXAMPLE 2

Hydrazinolysis of phthalimidoaminoindans [1]

A mixture 3.5mmol of phthalimidoaminoindan (as  
 10    prepared in Example 1) and 60% excess of 64% N<sub>2</sub>H<sub>4</sub>.H<sub>2</sub>O  
       in 40 ml of abs. ethanol was refluxed with stirring  
       for 1.5 hrs. After cooling and filtration the mother  
       liquor was evaporated and the substance was extracted  
       by reflux with 50ml of ethyl acetate. The solvent was  
 15    evaporated. The residue was dissolved in 15ml of  
       ether and gas HCl in ether (15ml pH<1) was added with  
       stirring. The residue was filtered.

In this way the following compounds were prepared;

20



25

$m=3$  (2709) recrystallized from ethyl acetate/ethanol (1.6:1), 82% yield, mpt 153-154°C.

30

<sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.60-7.39 (m, 4H), 4.91-4.82 (m, 1H), 3.28-3.02 (m, 6H), 2.67-2.58 (m, 1H), 2.34-2.26 (m, 1H); 2.17-2.10 (m, 2H).  
 IR (KBr, disc), cm<sup>-1</sup> 750, 1606, 1512, 3000-2500, 1444, 2700-2400, 3250.

35

m/z 190MH<sup>+</sup> (free base)

Anal. Calc. for C<sub>12</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>2</sub>, C 54.75%, H 7.00%, Cl 26.94%, N 10.65%

-19-

Found. C 55.06%, H 7.82%, Cl 26.00%, N 11.31%

m=4 (2710) recrystallized from ethyl acetate/ethanol (1.6:1), 83% yield, mpt 214-216°C(decomp).

5

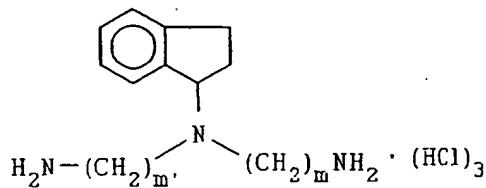
<sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.56-7.34 (m, 4H), 4.86-4.81 (m, 1H), 3.21-2.98 (m, 6H), 2.60-2.53 (m, 1H), 2.30-2.23 (m, 1H), 1.82-1.73 (m, 4H).

m/z 205MH<sup>+</sup> (free base).

10

and compounds;

15



m=m'=4 (2711)

was prepared by dissolution in water and stirring with  
20 Norit. After filtration and evaporation of water the residue was triturated with ether and crystallized from iso-propanol-ethanol 2:1, 45% yield.

25

<sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.55-7.37 (m, 4H), 5.24-5.21 (m, 1H), 3.20-2.89 (m, 10H), 2.57-2.51 (m, 1H), 2.39-2.32 (m, 1H), 1.90-1.56 (m, 8H).

IR (KBr, disc), cm<sup>-1</sup> 770-735, 1480-1440: 3000-2800, 1600, 1500, 3000, 2500, 2000, 1600-1575

m/z 275MH<sup>+</sup> (free base)

30

Anal. Calc. for C<sub>1</sub>H<sub>32</sub>Cl<sub>3</sub>N<sub>3</sub>, C 53.20%, H 8.40%, Cl 27.45%, N 10.95%

Found. C 53.01%, H 8.08%, Cl 28.84%, N 11.16%.

m=m'=4 (R)-enantiomer of 2711, (2726)

35

The above procedure was repeated using (R)-aminoindan as the starting material and recrystallizing from ethanol-isopropanol. Yield 57%, mpt > 280°C.

-20-

<sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.65-7.40 (m, 4H), 5.25 (m, 1H), 3.35-2.90 (m, 10H), 2.57 (m, 1H), 2.41 (m, 1H), 2.05-1.60 (m, 8H).

IR (KBr, disc), cm<sup>-1</sup> 3000-2850, 2046, 2010, 1616, 1606, 5 1532, 1512, 1470, 1446, 1017, 974, 775, 747.

m/z 276 (MH<sup>+</sup>, 100, free base)

Anal. Calc. for C<sub>17</sub>H<sub>32</sub>Cl<sub>3</sub>N<sub>3</sub>, C 53.06%, H 8.38%, Cl 27.64%, N 10.92%

Found. C 52.35%, H 8.46%, N 10.85%.

10 [alpha]<sub>D</sub> = -6.0°(H<sub>2</sub>O)

m=m'=4, (S)-enantiomer of 2711, (2727)

The above procedure was repeated using (S)-aminoindan as the starting material. Yield 56%, mpt > 280°C.

15 Spectral properties were identical to 7262 above.

[alpha]<sub>D</sub> = +6.4°(H<sub>2</sub>O)

20 Similarly, the enantiomers of other compounds of general formula I may be made by using the corresponding enantiomeric 1-aminoindan as the starting compound.

m=3, m'=4 (2722) 45% yield

25 was prepared by dissolution in water and stirring with Norit. After filtration and evaporation of water the residue was triturated with ether and crystallized from iso-propanol-ethanol 2:1, 45% yield, mpt 227-228°C.

30 <sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.56-7.39 (m, 4H), 5.28-5.26 (m, 1H), 3.32-2.97 (m, 10H), 2.60-2.54 (m, 1H), 2.40-1.62 (m, 7H).

IR (KBr, disc), V, cm<sup>-1</sup> 770-735, 1480-1440: 3200-2800, 1600, 1500, 3000, 2500, 2000, 1600-1575.

35 m/z 261MH<sup>+</sup> (free base)

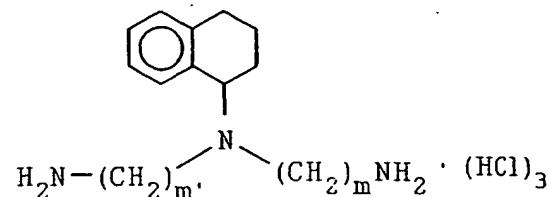
Anal. Calc. for C<sub>16</sub>H<sub>30</sub>Cl<sub>3</sub>N<sub>3</sub>, C 51.82%, H 8.16%, Cl 28.69%, N 11.33%

-21-

Found. C 51.34%, H 7.77%, Cl 29.85%, N 11.63%.

and compounds

5



10

$m=m'=4$  (2728)

The above procedure was repeated using 1-aminotetralin as the starting material.

15  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ ), delta, ppm: 7.53 (m, 1H), 7.48-7.33 (m, 3H), 5.04 (t, 1H), 3.50-2.65 (m, 10H), 2.35 (m, 1H), 2.15-1.40 (m, 11H).

IR (KBr, disc), V,  $\text{cm}^{-1}$  3000-2850, 2014, 1616, 1600, 1534, 1437, 1408, 1012, 773, 754.

$m/z$  290 ( $\text{MH}^+$ , 100, (free base)

20 Anal. Calc. for  $\text{C}_{18}\text{H}_{34}\text{Cl}_3\text{N}_3$ , C 54.21%, H 8.59%, Cl 26.67%, N 10.54%

Found. C 54.33%, H 8.84%, Cl 26.17%, N 10.65%.

### EXAMPLE 3

25

#### 3A. Protection of secondary amines with $\text{BOC}_2\text{O}$ [1].

A solution of 16mmol of a secondary amine of Formula IA or IB and 24mmol of  $\text{BOC}_2\text{O}$  in 50ml of dichloromethane 30 was stirred at R.T. for 3 hours. The reaction mixture was washed with 5% NaOH, dried, and evaporated. The residue was purified by column chromatography on Kieselgel. Eluent: hexane-ethyl acetate 2:1. Yield 85-95%.

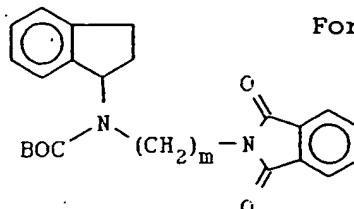
35

-22-

In this manner the following compounds were prepared

5

Compounds of  
Formula II



m=3 or m=4.

10

m=3;

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ), delta, ppm: 7.82-7.70 (m, 4H), 7.14-7.05 (m, 4H), 5.73 and 5.25 (broad s 1H), 3.65-1.28 (m, 19H).

15

m=4:

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ), delta, ppm: 7.81-7.70 (m, 4H), 7.13-7.00 (m, 4H), 5.72 and 5.25 (broad s 1H), 3.65-1.27 (m, 21H).

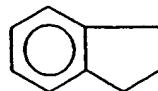
20

3B. Hydrazinolysis of BOC phthalimidoaminoindans [1].

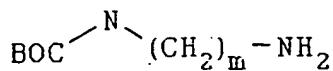
A mixture of 50mmol of BOC-phthalimidoaminoindan of Formula IIA and 65mmol of 64%  $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$  in 300ml of absolute ethanol was stirred at bath temperature 50°C for 10 hours. After cooling and filtration the mother liquor was evaporated. The residue was distributed in a mixture of ether-water. The ether phase was dried and evaporated, the residue was purified on Kieselgel. Eluent: dichloromethane-methanol-conc. ammonia 65:10:1. Yield 70-80%.

- 23 -

In this manner the following compounds were prepared;



5



### Compounds of Formula III

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.21-7.13 (m, 4H), 5.78 and  
5.27 (broad s, 1H), 3.28-1.21 (m, 19H).

$m=4$  :

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.20-7.14 (m, 4H), 5.77 and  
5.27 (broad s, 1H), 3.19-1.20 (m, 21H).

### 3C. Alkylation of primary amines.

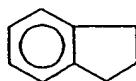
A mixture of 41.4mmol of a primary amine of Formula III, 82.8mmol of  $\text{Cl}(\text{CH}_2)_{m-1}\text{CN}$  and 124mmol of  $\text{K}_2\text{CO}_3$ , in 120ml of acetonitrile was refluxed with stirring for 3 hours, then an additional 41.4mmol of  $\text{Cl}(\text{CH}_2)_{m-1}\text{CN}$  was added, and the mixture was refluxed for 4 hours.

After addition of a further 82.8mmol of  $\text{Cl}(\text{CH}_2)_{m-1}\text{CN}$  the reaction mixture was refluxed for 3 hours. After cooling, filtration and evaporation, the residue was purified by column chromatography on Kieselgel.

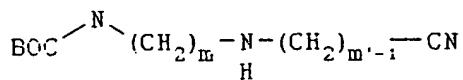
Eluent: dichloromethane-methanol 95:5. Yield 60-65%. m  
is 3 or 4 depending on the compound being synthesized.

30

In this manner the following compounds were prepared:



35



## Compounds of Formula IV

-24-

$m=3, m'=4$

$^1\text{H-NMR}(\text{CDCl}_3)$ , delta, ppm: 7.21-7.15 (m, 4H), 5.70 and 5.30 (broad s, 1H), 2.98-1.25 (m, 25H).

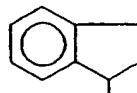
5       $m/z$  258MH $^+$

3D. Protection of secondary amines with BOC<sub>2</sub>O.

A solution of 16mmol of a secondary amine of Formula  
 10 IVA or IVB and 24mmol of BOC<sub>2</sub>O in 50ml of dichloromethane was stirred at R.T. for 3 hours. The reaction mixture was washed with 5% NaOH, dried, and evaporated. The residue was purified by column chromatography on Kieselgel. Eluent: hexane-ethyl acetate 2:1. Yield 85-95%.

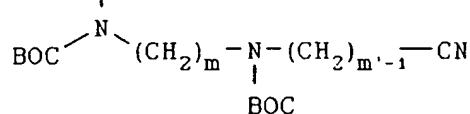
15      In this manner the following compounds were prepared;

20



Compounds of  
Formula V

$m=3, m'=4$



25

$^1\text{H-NMR}(\text{CDCl}_3)$ , delta, ppm: 7.21-7.16 (m, 4H), 5.78 and 5.28 (broad s, 1H), 3.10-1.24 (m, 34H).

3E. Reduction of nitriles with LiAlH<sub>4</sub>

30

To a suspension 4.0g of LiAlH<sub>4</sub> in 150ml of ether 5.8mmol a nitrile of Formula VB in 50ml of ether was added with stirring in an ice-bath, the suspension was then stirred without ice-bath for 0.5hrs. Excess of 35 LiAlH<sub>4</sub> was destroyed followed by addition of 4.0ml of water, 4.0ml of 10% NaOH and 12.0ml of water with cooling. The organic phase was decanted and additional

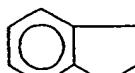
-25-

amount of the substance was extracted by dichloromethane. The combined organic phases were washed, dried and evaporated. The residue was purified by column chromatography on Kieselgel.

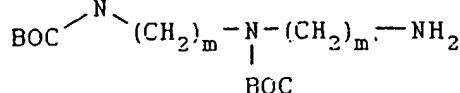
5      Eluent: dichloromethane-methanol - conc. ammonia 65:10:1. Yield 60-70%.

In this manner the following compounds were prepared;

10



Compounds of  
Formula VI



15      m=3, m'=4

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.22-7.14 (m, 4H), 5.78 and 5.30 (broad s, 1H), 3.04-1.26 (m, 36H).

20

3F. Deprotection of N-BOC derivatives.

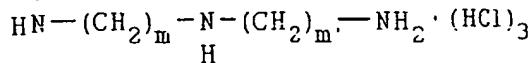
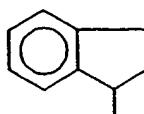
An excess of HCl in ether (18ml, pH<1) was added to a solution 2.5mmol of an N-BOC derivative of Formula VI in 6ml of methanol. The mixture was stirred at R.T.

25      for 4 hours. The precipitate was collected by filtration and washed with ether.

30

In this manner the following compounds were prepared;

35



-26-

m=3, m'=4 yield 50% mpt 239-240°C (2720).

<sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.56, 7.34 (m, 4H), 4.87-4.83 (m, 1H), 3.23-2.98 (m, 10H), 2.63-2.53 (m, 1H), 2.30-2.22 (m, 1H), 2.15-2.08 (m, 2H), 1.82-1.71 (m, 4H).

5 IR (KBr, disc), cm<sup>-1</sup> 770-735, 1600, 1500, 2000, 2300-2700, 2500, 3000, 3400, 3500.

m/z 262 (MH<sup>+</sup>, 100, free base)

Anal. Calc. for C<sub>16</sub>H<sub>30</sub>Cl<sub>3</sub>N<sub>3</sub> 0.7H<sub>2</sub>O\*, C 50.12%, H 8.18%, Cl 27.74%, N 10.96%

10 Found. C 50.16%, H 7.98%, Cl 28.09%, N 11.17%.

m=4, m'=3 (2724) 45% yield, mpt 237-238°C

<sup>1</sup>H-NMR (D<sub>2</sub>O), delta, ppm: 7.67-7.40 (m, 4H), 4.90-4.86

15 (m, 1H), 3.21-3.01 (m, 10H), 2.71-2.56 (m, 1H), 2.33-2.25 (m, 1H), 2.17-2.09 (m, 2H), 1.82-1.34 (m, 4H).

IR (KBr, disc), cm<sup>-1</sup> 750, 1608, 1500, 2700-2250, 2943, 2500, 2042

m/z 262MH<sup>+</sup> (free base)

20 Anal. Calc. for C<sub>16</sub>H<sub>30</sub>Cl<sub>3</sub>N<sub>3</sub> 0.7H<sub>2</sub>O\* C 50.12%, H 8.18%, Cl 27.74%, N 10.96%,

Found. C 49.10%, H 7.81%, Cl 27.68%, N 11.20%.

\* water content determined by Karl Fischer analysis.

25

EXAMPLE 4

4A. Alkylation of primary amines.

30 A mixture of 41.4mmol of a primary amine of Formula VI, 82.8mmol of Cl(CH<sub>2</sub>)<sub>m-1</sub>CN and 124mmol of K<sub>2</sub>CO<sub>3</sub>, in 120ml of acetonitrile was refluxed with stirring for 3 hours, then an additional 41.4mmol of Cl(CH<sub>2</sub>)<sub>m-1</sub>CN was added, and the mixture was refluxed for 4 hours.

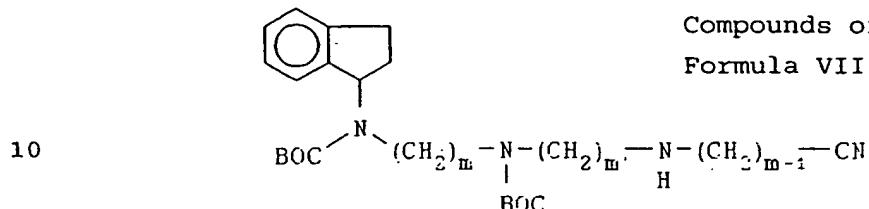
35 After addition of a further 82.8mmol of Cl(CH<sub>2</sub>)<sub>n</sub>CN the reaction mixture was refluxed for 3 hours. After cooling, filtration and evaporation the residue was

-27-

purified by column chromatography on Kieselgel.

Eluent: dichloromethane-methanol 95:5. Yield 60-65%. m is 3 or 4 depending on the compound being synthesized.

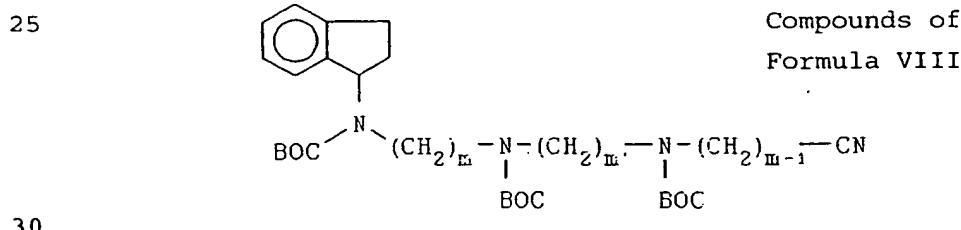
5 In this manner the following compounds were prepared;



4B. Protection of secondary amines with BOC<sub>2</sub>O [1].

15 A solution of 16mmol of a secondary amine of Formula VIIA or VIIIB and 24mmol of BOC<sub>2</sub>O in 50ml of dichloromethane was stirred at R.T. for 3 hours. The reaction mixture was washed with 5% NaOH, dried, and evaporated. The residue was purified by column chromatography on Kieselgel. Eluent: hexane-ethyl acetate 2:1. Yield 85-95%.

In this manner the following compounds were prepared;



4C. Reduction of nitriles with LiAlH<sub>4</sub>.

To a suspension 4.0g of LiAlH<sub>4</sub> in 150ml of ether 35 5.8mmol a nitrile of Formula VIIIB in 50ml of ether was added with stirring in an ice-bath, the suspension was then stirred without ice-bath for 0.5hrs. Excess

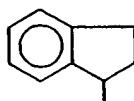
-28-

of LiAlH<sub>4</sub> was destroyed followed by addition of 4.0ml of water, 4.0ml of 10% NaOH and 12.0ml of water with cooling. The organic phase was decanted and additional amount of the substance was extracted by dichloromethane. The combined organic phases were washed, dried and evaporated. The residue was purified by column chromatography on Kieselgel. Eluent: dichloromethane-methanol - conc. ammonia 65:10:1. Yield 60-70%

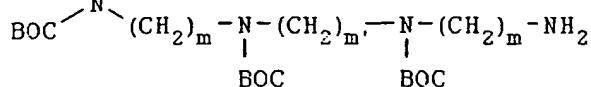
10

In this manner the following compounds were prepared;

15



Compounds of  
Formula VIII



BOC BOC

4D. Deprotection of N-BOC derivatives.

20

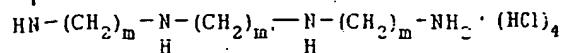
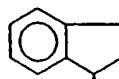
An excess of HCl in ether (18ml, pH<1) was added to a solution 2.5mmol of an N-BOC derivative of Formula VIII in 6ml of ether. The mixture was stirred at R.T. for 4 hours. The precipitate was collected by filtration and washed with ether. The salt was stirred in water with Norit. After filtration and evaporation the residue was triturated with methanol, filtered and washed with ether.

30

-29-

In this manner the following compounds were prepared;

5



10       $m=3, m'=4$  (2721) mpt  $>280^\circ\text{C}$ .

$^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ ), delta, ppm: 7.56-7.35 (m, 4H), 4.88-4.85 (m, 1H), 3.24-2.98 (m, 14H), 2.63-2.54 (m, 1H), 2.30-2.33 (m, 1H), 2.16-2.06 (m, 4H), 1.79-1.77 (m, 4H).  
 $m/z$  319319MH\*

15

$m=4, m'=3$  (2725) mpt  $>280^\circ\text{C}$ .

$^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ ), delta, ppm 7.56-7.34 (m, 4H), 4.86-4.83 (m, 1H),

3.21-3.02 (m, 14H), 2.61-2.53 (m, 1H), 2.30-2.22 (m, 1H),

20      2.16-2.19 (m, 2H), 1.81-1.73 (m, 8H).

IR (KBr, disc),  $\text{cm}^{-1}$  750, 1610, 1500, 2700-2250 (N\*HR),

3000, 2500, 2000 (NH<sub>3</sub>\*)

$m/z$  333MH\* (free base)

Anal. Calc. for  $\text{C}_{20}\text{H}_{40}\text{Cl}_4\text{N}_4$  0.5 $\text{H}_2\text{O}$  C 49.20%, H 8.20%, Cl

25      29.10%, N 11.50%,

Found. C 47.82%, H 8.39%, Cl 29.52%, N 11.99%.

\* water content determined by Karl Fischer analysis.

30

### EXAMPLE 5

#### A. 1,3-Indandione Dioxime

35      A mixture of 75 g of potassium carbonate, 30 g of hydroxylamine hydrochloride, 15 g of 1,3-indandione and 300 mL of 95% ethanol was heated to reflux with stirring for 15 min at which time it was poured into

-30-

400 mL of ice. The resulting precipitate was collected by filtration, washed with cold water and dried in vacuo to give 17.9 g of the title compound as an amorphous solid. NMR ( $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ ): 7.42-7.76 (m, 5 4H); 3.36 (s, 2H).

B. 1,3 Diaminoindan (cis/trans)

To a solution of 20 g of a 1,3-indandione dioxime in 10 L of absolute ethanol was cautiously added 160 g of sodium in portions during 1 hr (at such a rate to maintain reflux). After disappearance of the sodium, 300 mL of water was slowly added and the solution concentrated in vacuo to remove most of the ethanol. 15 The resulting solution was acidified with conc. hydrochloric acid to pH 1-2 followed by extraction with methylene chloride to recover unreacted starting material. The aqueous layer was basified with 10% sodium hydroxide to pH 12 and extracted with methylene 20 chloride which gave 11.7 grams of crude 1,3-diaminoindan upon solvent removal in vacuo. Purification of this material by flash column 25 chromatography eluting with 95% ethanol/ammonium hydroxide (400:16) gave 8.75 g of the title compound as an approximately 60/40 mixture of cis to trans isomers.

C. cis-N,N'-Diacetyl-1,3-diaminoindan (2717)

30 To a solution of 17.55 g of cis/trans-1,3-diaminoindan in 102 mL of pyridine was slowly added 102 mL of acetic anhydride. After 17 hrs the reaction mixture was 35 added to 250 mL of water and 300 mL of methylene chloride. The insoluble precipitate was isolated from this three-phase mixture by filtration and dried to

-31-

give 8.7 g of crude title compound which was recrystallized from ethanol to give 5.4 g pure material.

5       $^1\text{NMR}$  ( $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ ) delta: 7.3 (s, 4H); 5.3 (m, 2H);  
2.0 (s, 6H); 2.9 and 1.7 (m, 2H).

D. trans-N,N'-Diacetyl-1,3-diaminoindan (2718)

10     The combined methylene chloride extracts from the above example were concentrated in vacuo, suspended in 100 mL of water and basified with 10% sodium hydroxide to pH 12. Evaporation of the repeated methylene chloride extracts gave 9.4 g of crude N,N'-diacetyl-1,3-diaminoindan as a 35:65 cis/trans mixture. The 15 title compound (3.5 g) was isolated by flash column chromatography eluting with ethyl acetate/ethanol (95:5).

20       $^1\text{NMR}$  ( $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ ) delta: 7.35 (m, 4H); 5.59 (m, 2H); 2.33 (t, 2H); 2.02 (s, 6H).

E. cis-1,3-Diaminoindan hydrochloride (2715)

25     A solution of 100 mg of cis-N,N'-diacetyl-1,3-diaminoindan in 4 mL of 5% hydrochloric acid was heated at reflux for 6 hrs at which time it was cooled and 10% sodium hydroxide was added to pH 12-13. The combined methylene chloride extracts were evaporated to dryness to give 65 mg of crude diamine which was treated with methylene chloride and etheric hydrogen 30 chloride to give the title compound (35 mg).

35       $^1\text{NMR}$  ( $\text{CD}_3\text{OD}$ ) delta: 7.48 (m, 4H); 4.58 (d, d, 2H); 1.74, 3.05 (m, 2H).

F. trans-1,3-Diaminoindan hydrochloride (2716)

35     The title compound was prepared according to the method of the above example 5E, except that trans-

-32-

N,N'-diacetyl-1,3-diaminoindan was used as starting material.

<sup>1</sup>NMR (CD<sub>3</sub>OD) delta: 7.35 (m, 4H); 4.55 (t, 2H), 2.15 (t, 2H).

5

EXAMPLE 6

6A. Alkylation of 1,3-diaminoindan dihydrochloride

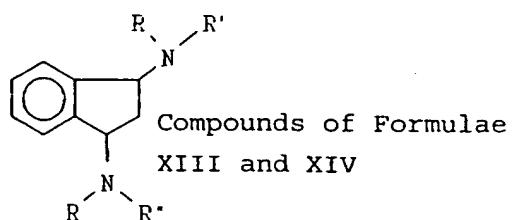
10

A mixture 14.9mmol of 1,3-diaminoindan dihydrochloride, 42.0mmol of 4-chlorobutyronitrile and 84.0mmol of K<sub>2</sub>CO<sub>3</sub>, in 50ml of acetonitrile was refluxed for 3 hrs. Then an additional 84.0mmol of 4-chlorobutyronitrile was added, and the mixture was refluxed for 4 hrs. After cooling and filtration the mother liquor was evaporated. The residue and 42.0mmol of BOC<sub>2</sub>O were dissolved in 150ml of dichloromethane and stirred at R.T. overnight. The reaction mixture was washed with 5% NaOH, dried, and evaporated. The residue was purified by column chromatography on Kieselgel, eluting with hexane-ethyl acetate (2:1) to isolate the BOC-mono-alkylated (XIII) and di-alkylated (XIV) products.

25

In this manner the following compounds were prepared;

30



cis R=BOC, R'=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CN, R''=H: IR (neat): 2245cm<sup>-1</sup>

35

-33-

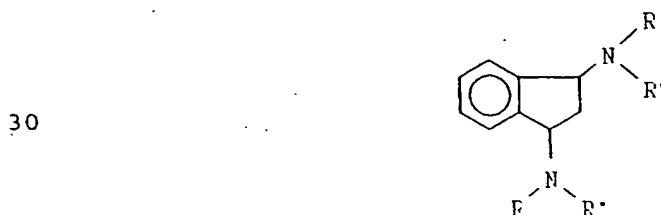
cis R=BOC, R'=R''=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CN: IR (neat): 2245cm<sup>-1</sup>

5 trans R=BOC, R'=R''=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CN: IR (neat): 2245cm<sup>-1</sup>

6B. Reduction of nitriles with LiAlH<sub>4</sub>

10 To a suspension 4.0g of LiAlH<sub>4</sub> in 150ml of ether  
 5.8mmol a nitrile of Formula XIII or XIV in 50ml of  
 ether was added with stirring in an ice-bath, the  
 suspension was then stirred without ice-bath for  
 15 0.5hrs. Excess LiAlH<sub>4</sub> was destroyed followed by  
 addition of 4.0ml of water, 4.0ml of 10% NaOH and  
 12.0ml of water with cooling. The organic phase was  
 decanted and an additional amount of the substance was  
 extracted by dichloromethane. The combined organic  
 20 phase was washed, dried and evaporated. The residue  
 was purified by column chromatography on Kieselgel.  
 Eluent: dichloromethane-methanol - conc. ammonia  
 65:10:1.

25 In this manner the following compounds were prepared;



cis R=BOC, R'=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, R''=H:

35

-34-

cis R=BOC, R'=R''=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>:  
m/z 491MH<sup>+</sup>

5

trans R=BOC, R'=R''=CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>:

6C. cis-N-(4-aminobutyl)-1,3-diaminoindan trihydrochloride (2731):

10

A solution of the above di-BOC derivative in methanol/ether was treated with gaseous hydrogen chloride for 6 hrs at RT. The precipitate was isolated by filtration and washed with ether.

15

A solution of this crude title compound (0.22g) in 15ml of methylene chloride/water (2:1) was again treated with BOC anhydride (0.62g) and 0.28g of potassium carbonate at 50°C for 20 min. The organic phase was separated, washed with 5% sodium hydroxide and evaporated to dryness. Flash column

20

chromatography on silica eluting with hexane/ethyl acetate (2:1) gave 170mg of the tri-BOC derivative.

Acidolysis was accomplished with 1ml of trifluoroacetic acid at RT during 20 min. After

25

evaporation of the trifluoroacetic acid, the title compound (41mg) was isolated from methanol/ether after treatment with hydrogen chloride gas.

30

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.85-7.80 (m, 1H), 7.68-7.56 (m, 3H), 4.97-4.89 (m, 2H), 3.30-3.18 (m, 3H), 3.03-2.98 (m, 2H), 2.43-2.37 (m, 1H), 1.98-1.77 (m, 4H).  
m/z 220MH<sup>+</sup> (free base)

35

6D. trans-N,N'-(Bis-4-aminobutyl)-1,3-diaminoindan tetrahydrochloride (2732):

A solution of the above di-BOC derivative in methylene

-35-

chloride was treated with BOC-anhydride at RT for 3hrs at which time the reaction mixture was washed with 5% sodium hydroxide and concentrated to dryness. The residue was purified by flash column chromatography on 5 silica eluting with hexane/ethyl acetate (2:1) to give the tetra-BOC derivative. Acidolysis was accomplished with 1ml of trifluoroacetic acid at RT during 20 min. After evaporation of the trifluoroacetic acid, the title compound was isolated from methanol/ether after 10 treatment with hydrogen chloride gas.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), delta, ppm: 7.90-7.87 (m, 2H), 7.62-7.59 (m, 2H), 5.23-5.20 (m, 2H), 3.30-3.15 (m, 4H), 3.02-2.98 (m, 4H), 2.91-2.88 (m, 2H), 1.96-1.76 (m, 8H).  
15 m/z 291MH<sup>+</sup>

EXAMPLE 7:

Preparation of (XVIII)

20 A mixture of racemic aminoindan (12.38g, 0.093 mol), potassium carbonate (12.84g, 0.093 mol), N-(3-Bromopropyl)-phthalimide (24.92g, 0.093 mol) and acetonitrile (120mL) was stirred and heated at 50-55°C under nitrogen for 10 hours. The mixture was then 25 cooled and filtered under vacuum. The mother liquor was evaporated at reduced pressure to give 30.4g of crude product which was purified by flash chromatography to give 21.27g (71.5% yield) of an off-white solid.

30

Preparation of (XIX)

A mixture of XVIII (17.45g, 0.055 mol), 4-bromobutyronitrile (8.1g, 0.055 mol), potassium carbonate (30.19g, 0.218 mol) and acetonitrile (440mL) 35 was stirred and heated at reflux under nitrogen for 5 hours. The mixture was cooled to 60°C and additional 4-bromobutyronitrile (32.43g, 0.219 mol) was added. The mixture was now stirred and heated at reflux under

-36-

nitrogen for 20 hours. The mixture was then cooled and filtered and the mother liquor was evaporated under vacuum. The residue was heated under high vacuum to remove the excess 4-bromobutyronitrile and 5 the residual viscous oil was purified by flash chromatography to give 17.80g (84% yield).

10       $^1\text{H}$  NMR  $\delta$  (DMSO): 7.83 (s, 4H, Ph), 7.28-7.05 (m, 4H, Ph), 4.46 (t, 1H, Cl-H), 3.67 (m, 1H, C3-H), 3.47 (m, 1H, C3-H'), 2.75 (m, 2H), 2.60-2.30 (m, 6H), 2.05 (m, 1H), 1.95 - 1.60 (m, 5H) ppm.

Preparation of (XX)

15      A mixture of XIX (17.45g, 0.045 mol), 55% hydrazine hydrate (4.25g, 0.073 mol, 60% excess) and absolute ethanol (550mL) was stirred and heated at reflux under nitrogen for 4 hours. On cooling a white solid precipitated; it was filtered and washed with cold ethanol (3 x 75mL). The combined filtrate was 20 evaporated under vacuum to give a crude yellow solid. This crude solid was dissolved in a mixture of saturated brine (200mL) and hot ethyl acetate (300mL) and the layers were separated. The aqueous layer was reextracted with ethyl acetate (3 x 100mL). The 25 combined organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and solvent was removed at reduced pressure to give 10.8g of a yellow oil. The crude product was purified by flash chromatography to give 7.65g (66% yield) of a yellow oil.

30       $^1\text{H}$  NMR  $\delta$  (DMSO): 7.30-7.10 (m, 4H, Ph), 4.45 (t, 1H, Cl-H), 2.95-2.65 (m, 2H), 2.60-2.30 (m, 8H), 2.05 (m, 1H), 1.86 (m, 1H), 1.70 (m, 2H), 1.50 (m, 2H) ppm  
MS: 259 (NH<sup>+</sup>, 100)

35      Preparation of (XXI)

A solution of XX (7.65g, 0.030 mol) and di-tert-butyl dicarbonate (9.80g, 0.045 mol) in methylene chloride

-37-

(400mL) was stirred at 20°C under nitrogen for 8 hours. The reaction mixture was then washed with 5% aqueous NaOH solution (150mL) and the layers were separated. The aqueous layer was reextracted with 5 methylene chloride (3 x 75mL) and the combined layer was dried and evaporated to 14.5 grams of a yellow oil. The crude product was purified by flash chromatography to give 10.15g (95% yield) of a yellow oil.

10

Preparation of (XXII)

To a suspension of LAH (19.35g, 0.51 mol) in anhydrous ether (730mL) was added IV (10.0g, 0.028 mol) dissolved in anhydrous ether (230mL). The addition 15 was carried out at 0-5°C with stirring under a nitrogen atmosphere. After the addition was complete, the suspension was stirred at 5°C for an additional 30 minutes and then it was stirred at 25°C under nitrogen for 3 hours. The mixture was now cooled to 5°C and 20 the excess LAH was decomposed by the addition of water (110mL), 10% sodium hydroxide solution (320mL) and more water (75mL). Ethyl acetate (365mL) was then added to the stirred mixture and it was filtered through a celite pad. The pad was washed with ethyl acetate (3 x 150mL) and the layers were separated. 25 The aqueous layer was reextracted with ethyl acetate (150mL). The combined ethyl acetate layer was dried ( $\text{Na}_2\text{SO}_4$ ) and solvent was removed under vacuum to give 9.27g (92% yield) of a viscous yellow oil.

30

Preparation of (XXIII)

A mixture of XXII (7.9g, 0.022 mol), potassium carbonate (3.03g, 0.022 mol), 35 N-(3-Bromopropyl)-phthalimide (5.89g, 0.022 mol) and acetonitrile (175mL) was stirred and heated at 55-60°C under nitrogen for 7 hours. The mixture was then cooled and filtered under vacuum. The mother liquor

-38-

was evaporated at reduced pressure to give 12.3g of a viscous oil which was purified by flash chromatography to give 3.3g (28% yield) of a white solid.

5       Preparation of (XXIV)

A mixture of XXIII (3.0g, 5.47 mmol), 55% hydrazine hydrate (0.51g, 8.77 mmol, 60% excess) and absolute ethanol (120mL) was stirred and heated at reflux under nitrogen for 5 hours. It was then evaporated under vacuum to give a white solid which was dissolved in a mixture of saturated brine (70mL) and hot ethyl acetate (100mL). The layers were separated and the aqueous layer was reextracted with ethyl acetate (2 x 70mL). The combined organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and solvent was removed at reduced pressure to yield 2.25g (98% yield) of a viscous yellow semi-solid.

10      Preparation of (XXV)

A solution of XXIV (2.25g, 5.38 mmol) and di-tert-butyl dicarbonate (4.46g, 20.4 mmol) in methylene chloride (75mL) was stirred at 25°C under nitrogen for 22 hours. The reaction mixture was then washed with 5% aqueous NaOH solution (100mL) and the layers were separated. The aqueous layer was reextracted with methylene chloride (3 x 40mL) and the combined organic layer was dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent at reduced pressure gave 5.65 grams of a yellow oil which was purified by flash column chromatography to give 3.26g (98% yield) of a yellow oil.

15      Preparation of 3069

Ether saturated with HCl gas (30mL) was added to a solution of XXV (3.16g, 5.22 mmol) dissolved in methanol (60mL). The solution was stirred at 25°C for 3 1/2 hours. Solvents were removed under vacuum to give 2.29g of an off-white solid which was purified by

-39-

heating it in water (300mL) containing Norit (480mg) at 90-95°C for 5 minutes. The mixture was filtered hot through a celite pad and the pad was washed with hot water (3 x 150mL). The colorless filtrate was 5 evaporated under vacuum at 60°C. Hexane was added to the residue and solvent was removed under vacuum. Finally, methanol (100mL) was added to the residue. Its removal under reduced pressure gave 2.16g (91%) of a hygroscopic white solid.

10

Anal. calcd for  $C_{19}H_{38}Cl_4N_4 \cdot H_2O$ : C, 47.31; H, 8.36; Cl,

29.40; N, 11.62

Found: C, 47.71; H, 8.21; Cl, 29.25; N, 11.65

15

$^1H$  NMR  $\delta$  (DMSO): 7.62 (d, 1H, Ph), 7.58-7.40 (m, 3H, Ph), 5.28 (dd, 1H, Cl-H), 3.30-3.0 (m, 14H,), 2.58 (m, 1H, C2-H'), 2.40 (m, 1H, C2-H), 2.30-2.05 (m, 4H), 2.0-1.6 (m, 4H) ppm

20

MS : 319 ( $MH^+$ )

HPLC: 99%

EXAMPLE 8:

25

Preparation of II

A mixture of N,N-Bis-4-aminobutyl racemic aminoindan (compound no. 2711, 2.5g, 6.5mmol), N,N-di-tert-30 butoxycarbonylthiourea, (Iwanowicz E et al. Synthetic Communications (1993) 23, 1443), (3.5g, 13.0 mmol), triethyl amine (3.61g, 35.75 mmol) and dry DMF (19.5mL) was stirred at 0°C under nitrogen for an hour. The ice bath was removed and the mixture was 35 then stirred at 22-24°C under nitrogen for 22 hours. Ethyl acetate (200mL) was added and the mixture was filtered through a Celite pad. The pad was washed

-40-

with ethyl acetate (4 x 70mL). The combined filtrates were washed with water (200mL), sat. sodium chloride (200mL) and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent gave 6.2g of a viscous semi-solid. The crude product was 5 purified by flash chromatography using hexane/ethyl acetate 70/30 as eluent. This gave 3.5g (71% yield) of an off-white hygroscopic solid.

Preparation of III

10 A mixture of N-4-aminobutyl racemic aminoindan (2710, 3.33g, 12.0 mmol), N,N-di-tert-butoxycarbonylthiourea, (Iwanowicz E et al. Synthetic Communications (1993) 23, 1443), (3.32g, 12.0 mmol), triethylamine (4.85g, 15 48.0 mmol) and dry DMF (30mL) was treated and worked up according to the conditions used for the preparation of II. Removal of solvent gave 6.0g of a viscous oil/semi-solid. The crude product was purified by flash chromatography using methylene 20 chloride/methanol 94/6 as eluent. This gave 3.5g (65.5% yield) of a viscous brown oil.

Preparation of (N,N-di-(4-Guanidinobutyl)-aminoindan·  
3HCl (3042)

25 To a solution of II (3.0g, 3.95 mmol) dissolved in ether (10mL) was added ether saturated with HCl gas (10mL). A gummy oil precipitated. Then methanol (40mL) was added and the solution was stirred at 25°C 30 for 30 minutes. Solvents were removed under vacuum to give 3.2g of a white solid. It was purified by heating it in water (150mL) containing Norit (500mg) at 90-95°C for 5 minutes. The mixture was filtered hot through a Celite pad and the pad was washed with 35 hot water (2 x 100mL). The colorless filtrate was evaporated under vacuum at 60°C. Hexane was added to the residue and solvent was removed under vacuum.

-41-

Finally, methanol (100mL) was added to the residue. Its removal under reduced pressure gave a white solid (1.60g, 86%) which was dried at 40°C under high vacuum and stored in a desiccator over phosphorus pentoxide.

5

Anal. for C<sub>19</sub>H<sub>36</sub>C<sub>13</sub>N<sub>2</sub>: 2H<sub>2</sub>O:C, 45.2; H, 7.98; N, 19.42  
Found: C, 44.90, H, 6.65; N, 19.06  
<sup>1</sup>H NMR δ (D<sub>2</sub>O): 7.60-7.30 (m, 4H, Ph), 5.20 (dd, 1H, Cl-H)  
3.40-3.0 (m, 9H), 2.90 (M, 1H, C3-H), 2.52 (m, 1H, C2-H),  
10 2.36 (m, 1H, C2-H<sup>1</sup>), 2.0-1.4 (m, 8H) ppm.

FABMS: 360 (MH<sup>+</sup>), 396 (MH<sup>+</sup>+HCl).

IR (KBr): 3397, 1665, 1464, 1167, 766 cm<sup>-1</sup>.

15

HPLC: 96%

Preparation of (N-(4-Guanidinobutyl)-aminoindan·2HCl)  
(3043)

20

Ether saturated with HCl gas (15mL) was added to a solution of III (305g, 7.85 mmol) dissolved in ether (10mL). A gummy solid precipitated. Then methanol (50mL) was added and the solution was stirred at 25°C for 30 minutes. Solvents were removed under vacuum to give 3.3g of a white solid, which was purified by heating in water (180mL) containing Norit (560mg) at 90-95°C for 5 minutes. The mixture was filtered hot through a Celite pad and the pad was washed with hot water (2 x 100mL). The colorless filtrate was evaporated under vacuum at 60°C. Hexane was added to the residue and solvent was removed under vacuum. Finally, methanol (100mL) was added to the residue. Its removal under reduced pressure gave 2.14g (86%) of an extremely hygroscopic white solid which was dried at 25°C under high vacuum and stored in a desiccator over P<sub>2</sub>O<sub>5</sub>.

35

-42-

Anal. calcd. for  $C_{14}H_{24}Cl_2N_4 \cdot H_2O$ : C, 49.85; H, 7.77; N, 16.6  
Found: C, 49.11; H, 7.63; N, 16.70

<sup>1</sup>H NMR  $\delta$  (D<sub>2</sub>O) : 7.60-7.30 (m, 4H, Ph), 4.8 (m, 1H, Cl-H), 3.30-  
5 3.05 (m, 5H), 3.0 (m, 1H, C3-H), 2.55 (m, 1H, C2-H), 2.26 (m, 1H, C2-H) 1.80-1.60 (m, 4H) ppm

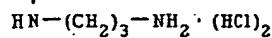
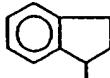
FABMS: 247 (MH<sup>+</sup>), 283 (MH<sup>+</sup>+HCl).

10 IR (KBr) : 3349, 3161, 2950, 2803, 1665, 1462, 1169, 765 cm<sup>-1</sup>.

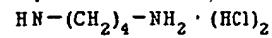
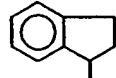
HPLC: 95%

## STRUCTURES OF COMPOUNDS

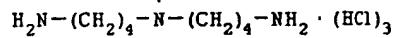
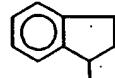
2709



2710



2711



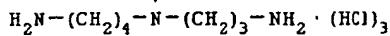
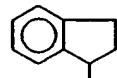
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(R)-2711

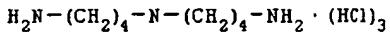
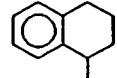
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(S)-2711

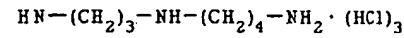
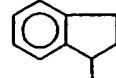
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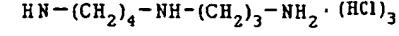
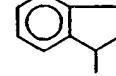
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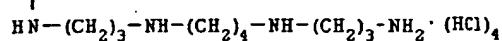
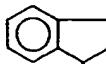
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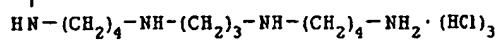
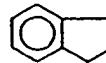
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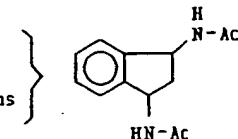


2725



2717

cis



2718

trans

}

2715

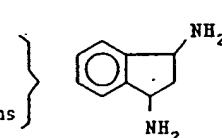
cis

}

2716

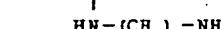
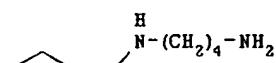
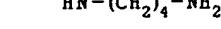
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}



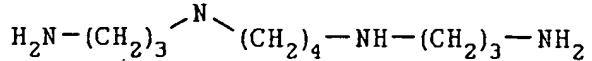
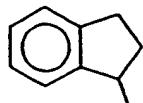
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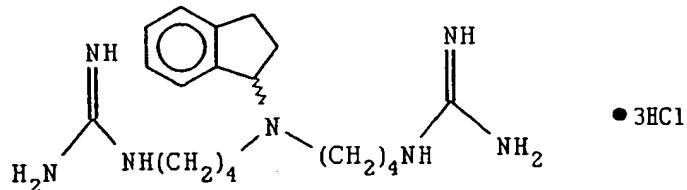


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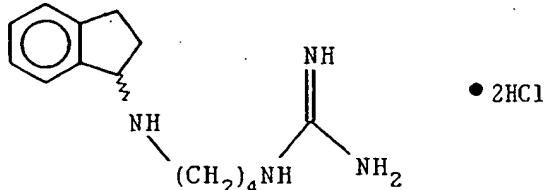
3069



3042



3043



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Names of Some Compounds

<u>Compound Number</u>	<u>Compound Name</u>
5      2709	N- (3-aminopropyl)-1-aminoindan
	2710      N- (4-aminopropyl)-1-aminoindan
	2711      racemic N,N-di(4-amino-n-butyl)-1-aminoindan
10     2726	(R)-N,N-di(4-amino-n-butyl)-1-aminoindan
	2727      (S)-N,N-di(4-amino-n-butyl)-1-aminoindan
15     2722	N- (4-amino-n-butyl)-N- (3-amino-n-propyl)-1- aminoindan
	2728      N,N-di(4-amino-n-butyl)-1-amino-1,2,3,4- tetrahydronaphthalene
20     2720	N- [N- (4-aminobutyl)-3-aminopropyl]-1- aminoindan or N- (1-indanyl)-N' - (4- aminobutyl)-1,3-diaminopropane
25     2724	N- [N- (3-aminopropyl)-4-aminobutyl]-1- aminoindan or N- (1-indanyl)-N' - (3- aminopropyl)-1,4-diaminobutane
30     2721	N- { [N- (3-aminopropyl)-4-aminobutyl)] -N' -3- aminopropyl}-1-aminoindan or N- (1-indanyl)- N' - [N- (3-aminopropyl)-4-aminobutyl]-1,3- diaminopropane
35     2725	N- { [N- (4-aminobutyl)-3-aminopropyl)] -N' -4- aminobutyl}-1-aminoindan or N- (1-indanyl)- N' - [N- (4-aminobutyl)-3-aminopropyl]-1,4- diaminobutane

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2717      cis N,N'-diacetyl-1,3-diaminoindan

2718      trans N,N'-diacetyl-1,3-diaminoindan

5        2715      cis 1,3-diaminoindan

2716      trans 1,3-diaminoindan

2731      N-(4-aminobutyl)-1,3-diaminoindan

10        2732      N,N'-di(4-aminobutyl)-1,3-diaminoindan

3069      N-(3-aminopropyl)-N-[N-(3-aminopropyl)-4-aminobutyl]-1-aminoindan

15        3042      N,N-di(4-guanidinobutyl)-1-aminoindan

3043      N-(4-guanidinobutyl)-1-aminoindan

## BIOLOGICAL EXAMPLES

## 1. Cultures of dissociated neonatal rat cerebellum

5       A. Reversal of NMDA induced cell death.

The cerebellum was aseptically dissociated from 6 or 7-day old rat pups and placed in a 15ml sterile plastic conical tube containing 3ml of Dulbecco's modified Eagle's medium (DMEM) with a high glucose concentration (1g/ml) and 2mM (v/v) L-glutamine and an antibiotic antimitotic mixture. The cerebella were then dissociated after 20-25 passages through a sterile 13 gauge, 10cm long stainless steel needle attached to a 5ml syringe with an inserted 45 micrometer pore nylon sieve. The dissociated cells were centrifuged at 200g for 5 minutes. The supernatant was discarded and the cells resuspended in medium enriched with 15% (v/v) heat inactivated fetal calf serum. Cell viability was determined by the tryptan blue exclusion test.

Cells were plated at a density of 200/mm<sup>2</sup> on poly-L-lysine coated surfaces. Poly-L-lysine coated glass coverslips were prepared at least one hour in advance of plating by immersing sterile coverslips in sterile distilled water solution containing 15 microgram/ml poly-L-lysine, and washing in sterile water just prior to use. The plated cells were covered with enriched medium and incubated at 37°C in an atmosphere of 5% CO<sub>2</sub> in air and 97% humidity. After three days in culture, the media was replaced with media containing the desired test compound. Each test compound was tested in duplicate. Toxic-dose response was determined for each compound over a range from 0.005-1000 micromole. Four groups were run in each set of experiments; I. Control, consisting of enriched media alone, II. N-methyl-D-aspartate (NMDA, 1mM for 3 hours) as

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the cytotoxic challenge,  
III. Test compound plus NMDA, and  
IV. Positive control, spermine, spermidine or  
putrescine  
5 (0.01 micromoles) plus NMDA.  
Nerve cell survival was evaluated by phase contrast  
microscopy and tryptan blue staining after 24 hours.

Results

10 The results are shown in Table 1 below. Surviving  
cells in Culture are measured relative to control  
(100%) as described above. Percent protection is the  
Cell Survival for the test compound minus the NMDA  
effect. Thus, maximal protection is 100% minus 30%  
15 NMDA effect i.e. 70%. The Effective Protection was  
calculated as the percent of the Percent Protection  
(X) divided by the maximal protection value (e.g. X x  
100/70).

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Table 1

COMPOUND	EXPERIMENTAL GROUP Dose ( $\mu$ M)	SURVIVING CELL IN CULTURE	PERCENT PROTECTION	EFFECTIVE PROTECTION
	Control NMDA Max protection Spermine + NMDA Spermidine + NMDA Putrescine + NMDA	100 30 68 78 30	70 38 48 0	100 54 69 0
(R)-1-aminoindan	0.005 0.010 0.100	80 30 28	50 0 -2	71 0 -
2709	0.005 0.010 0.100 1.000 10.00	26 53 59 43 38	-4 23 29 13 8	- 33 41 18* 11
2710	0.100 1.000	72 70	42 40	60 57
2711	0.005 0.010 0.100	74 68 62	44 38 32	63 54 46
2715	0.005 0.100 1.000	49 42 32	19 12 2	27 17 3
2716	0.005 0.010 0.100 1.000	65 30 25 30	35 0 -5 0	50 0 - 0
2720	0.005 0.010 0.100	72 38 32	42 8 2	60 11 3
2721	0.005 0.010	28 26	-2 -4	- -
2722	0.005 0.010	115 87	85 57	121 81
2724	0.005 0.010	95 87	65 57	93 81

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2725	0.005 0.010 0.100	72 38 32	42 8 2	60 11 3
2728	0.005 0.010	20 86	-10 56	- 80
2726	0.005 0.010	129 55	99 25	141 36
2727	0.005 0.010	30 55	0 25	0 36

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B: In Vitro Cell Toxicity

5 Toxic dose-response curves were compiled using the protocol described above. The TD<sub>50</sub> values calculated appear in Table 2 below.

10 Table 2

COMPOUND	TOXICITY TD <sub>50</sub> $\mu$ M
Spermine	2
Spermidine	2
Putrescine	300
15 (R)-1-aminoindan	175
2709	50
2710	30
2711	60
20 2715	10
2716	0.7
2720	0.2
2721	1
2722	20
25 2724	4
2725	20
2728	0.25
2726	1.7
2727	0.4

30

2. Global Brain Ischemia In Gerbils

35 Male mongolian gerbils, aged 2.5-5 months, housed 4-8 in a cage, were supplied freely with food and water and maintained at 24°C with a 12 hour day/night cycle.

-53-

For surgery the animals were anesthetized with halothane (1.5% in 100% O<sub>2</sub>) and the common carotid arteries exposed bilaterally through a midline ventral neck incision. Each artery was clamped for 5 minutes  
5 with aneurysm clips to produce global brain ischemia. The anesthesia was discontinued upon clamping. After 5 minutes the clamps were removed and the wound closed with skin clips.

10 For treatment, the test compound or vehicle was injected intra-peritoneally (ip) in a volume of 50 microlitres of solvent per 10g body weight. The first injection was given two minutes after clamp removal, and thereafter daily for the next 2 post-operative  
15 days (total of 3 injections).

Seven groups each of 4-8 animals were compared:  
I. Control; (sham- or unoperated and saline treated),  
II. Vehicle treated, unoperated (when solvent is other  
20 than saline),  
III. Ischemia - untreated or saline treated),  
IV. Ischemia - vehicle treated (when solvent is other  
than saline),  
V. Ischemia - Test compound treated, one sub-group per  
25 concentration tested,  
VI. Ischemia and pentobarbital (40 mg/kg) as positive control).

Analysis of neuronal damage was performed 14 days  
30 post-ischemia by counting pyramidal neurons throughout the CA1 layer of the anterior hippocampus in 4 micromolar thick (paraffin) coronal brain sections stained with hematoxylin and erosin.

35 The Results are shown in the Table 3 below. Percent Protection values represent the fraction of hippocampi protected from ischemia in a group of animals treated with the stated dose of compound.

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Table 3

	TEST COMPOUND (n)	DOSE (mg/kg)	% INTACT NEURONS	PERCENT PROTECTION
5	Control Ischemia Pentobarbital (8)		100 0	87.5
10	Spermine	10.0		60
15	Spermidine	10.0		42
20	Putrescine	10.0		41
25	(R) -1-aminoindan (4) (4) (4)	0.1 1.0 10.0		25.0 25.0 25.0
30	(S) -1-aminoindan (4) (4) (4)	0.1 1.0 10.0		0 50.0 75.0
35	2709 (4) 2710 (4) 2711 (4) 2715 (4) 2716 (4) 2720 (2) 2721 (8) 2722 (4) 2724 (4) 2725 (4)	1.0 10.0 1.0 10.0 1.0 10.0 1.0 10.0 1.0 10.0		12 31 25 37 50 86 70 75 50 - 58 12 67 50 25 12 56 0 25
40				

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2728	(5)	1.0		20
	(5)	10.0		80
	(5)	10.0		40
2726	(4)	10.0		50
5	2727	(7)	10.0	28.5

FOCAL CEREBRAL ISCHEMIA IN RATS

10

Ischemia was produced by intraluminal middle cerebral artery (MCA) occlusion in 4-month-old male Wistar rats. The surgery was performed under halothane anesthesia according to Longa et al. (Stroke, 20: 84-91, 1989). Briefly, the left common carotid artery (CCA) was exposed through a ventral neck incision and temporarily clamped, the pterygopalatine artery ligated, the external carotid artery (ECA) cut and a 4-0 nylon monofilament (its tips rounded by heating) was introduced and advanced about 18 mm through the ECA and the internal carotid artery into the anterior cerebral artery to block the origin of the MCA. The monofilament was then secured with a suture around the ECA, the clamp removed from the CCA and the anesthesia discontinued. After 3 h of ischemia without anesthesia, the rats were lightly anesthetized the monofilament withdrawn and re-perfusion commenced. Drugs: 10 mg/kg of 2711 were injected intraperitoneally 5 min. after beginning of re-perfusion and again once daily for the next 2 postoperative days (altogether 3 injections). Saline injected animals served as controls. Body weight was recorded just prior to surgery and then daily. Histology: Animals were killed 3 days after the occlusion

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and the brains were removed and fixed in buffered pH 7.4 formalin. Cross sections (5  $\mu\text{M}$  thick paraffin sections) were taken at 3 representative levels (4.5mm (A), 6.5mm (B) 5 and 10.5mm (C) anterior to the intraural line) and stained with hematoxylin and eosin. The damaged area, containing damaged pyknotic neurons in the parietal and olfactory cortex and in the striatum, was measured by 10 planimetry under the microscope. Tables 4 and 5 below show the effect of 2711 on the area of brain damage and body weight respectively.

Table 4

<u>Brain damage (<math>\text{mm}^2</math>)</u>			
	A	B	C
Saline	8.7 $\pm$ 2.5	15.2 $\pm$ 3.5	21.0 $\pm$ 4.7
TV-2711	1.4 $\pm$ 0.5	4.6 $\pm$ 3.3	7.4 $\pm$ 3.8

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Table 5

		Body Weight			
5					
Saline (%)	(6)	425±5 (100)	377±5 (89)	357±6 (84)	342±6 (81)
10 2711 (%)	(5)	430±3 (100)	396±6 (92)	384±5 (89)	379±6 (88)

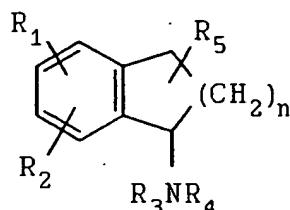
The effect of 2711 on the outcome of focal  
15 cerebral ischemia in rats in terms of damage  
to the brain (table 1) and effect on body  
weight (table 2). Results are expressed in  
mean±S.E.M. values.

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## What is claimed is:

1. A compound of the formula:

5



10

wherein n is 1 or 2;

R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, hydroxy, substituted or unsubstituted C<sub>1-4</sub> alkyl, substituted or unsubstituted C<sub>1-4</sub> alkoxy or halogeno;

15 R<sub>5</sub> is hydrogen, substituted or unsubstituted C<sub>1-4</sub> alkyl, amino or NR<sub>6</sub>R<sub>7</sub>;

R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> wherein m is from 0-5, y is from 0-5 and each x is independently from 1-5 and R<sub>11</sub> is hydrogen or C(NH)NH<sub>2</sub>;

20 provided that when R<sub>3</sub> and R<sub>4</sub> are both hydrogen, R<sub>5</sub> is amino or NR<sub>6</sub>R<sub>7</sub>; pharmaceutically acceptable salts and optically active isomers thereof.

25 2. The compound of claim 1, wherein n is 1.

3. The compound of claim 1, wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>5</sub> are hydrogen.

30 4. The compound of claim 1, wherein R<sub>3</sub> is (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub> and R<sub>4</sub> is hydrogen.

5. The compound of claim 4, wherein R<sub>11</sub> is hydrogen.

35 6. The compound of claim 4, wherein m is 3 or 4.

7. The compound of claim 4, wherein y is 0, 1 or 2.

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8. The compound of claim 4, wherein each x is 3 or 4.
9. The compound of claim 4, wherein y is greater than 1, and each x is 3 or 4.  
5
10. The compound of claim 4, wherein R<sub>11</sub> is C(NH)NH<sub>2</sub>.
11. The compound of claim 1, wherein both R<sub>3</sub> and R<sub>4</sub> are (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub>.  
10
12. The compound of claim 11, wherein R<sub>11</sub> is hydrogen.
13. The compound of claim 11, wherein m is 3 or 4.
14. The compound of claim 11, wherein y is 0, 1 or 2.  
15
15. The compound of claim 14, wherein y is 0.
16. The compound of claim 11, wherein R<sub>11</sub> is C(NH)NH<sub>2</sub>.  
20
17. The compound of claim 1, wherein R<sub>3</sub> and R<sub>4</sub> are hydrogen; and R<sub>5</sub> is amino or NR<sub>6</sub>R<sub>7</sub>.
18. The compound of claim 17, wherein m is 3 or 4; y is  
25 0, 1 or 2; and each x is 3 or 4.
19. The compound of claim 17, wherein R<sub>5</sub> is amino.
20. The compound of claim 17, wherein R<sub>5</sub> is NR<sub>6</sub>R<sub>7</sub>.  
30
21. The compound of claim 20, wherein R<sub>6</sub> is hydrogen; and R<sub>7</sub> is (CH<sub>2</sub>)<sub>m</sub>-[NH(CH<sub>2</sub>)<sub>x</sub>]<sub>y</sub>-NHR<sub>11</sub>.
22. The compound of claim 21, wherein m is 3 or 4; y is  
35 0; and R<sub>11</sub> is hydrogen.
23. The compound of claim 1, wherein R<sub>5</sub> is trans with

-60-

respect to NR<sub>3</sub>R<sub>4</sub>.

24. The compound of claim 1, wherein R<sub>5</sub> is cis with respect to NR<sub>3</sub>R<sub>4</sub>.

5

25. The compound of claim 1, wherein the ring carbon to which NR<sub>3</sub>R<sub>4</sub> is bound is in the R configuration.

10

26. The compound of claim 1, wherein the ring carbon to which NR<sub>3</sub>R<sub>4</sub> is bound is in the S configuration.

27. The compound of claim 1, selected from the group consisting of:

N-(3-aminopropyl)-1-aminoindan;

15

N-(4-aminopropyl)-1-aminoindan;

N,N-di(4-amino-n-butyl)-1-aminoindan;

(R)-N,N-di(4-amino-n-butyl)-1-aminoindan;

(S)-N,N-di(4-amino-n-butyl)-1-aminoindan;

N-(4-amino-n-butyl)-N-(3-amino-n-propyl)-1-aminoindan;

20

N,N-di(4-amino-n-butyl)-1-amino-1,2,3,4-tetrahydronaphthalene;

N-[N-(4-aminobutyl)-3-aminopropyl]-1-aminoindan;

N-[N-(3-aminopropyl)-4-aminobutyl]-1-aminoindan;

25

N-[N-(3-aminopropyl)-4-aminobutyl]-N'-3-aminopropyl]-1-aminoindan;

N-[N-(4-aminobutyl)-3-aminopropyl]-N'-4-aminobutyl]-1-aminoindan;

cis N,N'-diacetyl-1,3-diaminoindan;

30

trans N,N'-diacetyl-1,3-diaminoindan;

cis 1,3-diaminoindan;

trans 1,3-diaminoindan;

N-(4-aminobutyl)-1,3-diaminoindan;

35

N,N'-di(4-aminobutyl)-1,3-diaminoindan;

N-(3-aminopropyl)-N-[N-(3-aminopropyl)-4-aminobutyl]-1-aminoindan;

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N,N-di(4-guanidinobutyl)-1-aminoindan;  
N-(4-guanidinobutyl)-1-aminoindan,  
or a pharmaceutically acceptable salt thereof.

5      28. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

10     29. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable carrier is a solid and the pharmaceutical composition is a tablet.

15     30. The pharmaceutical composition of claim 28, wherein the therapeutically effective amount is from about 1 mg to about 1000 mg.

20     31. The pharmaceutical composition of claim 30, wherein the therapeutically effective amount is from about 10 mg to about 100 mg.

25     32. The pharmaceutical composition of claim 28, wherein the pharmaceutically acceptable carrier is a liquid and the pharmaceutical composition is an injectable solution.

30     33. The pharmaceutical composition of claim 32, wherein the therapeutically effective amount is from about 1 mg/ml to about 1000 mg/ml.

35     34. The pharmaceutical composition of claim 33, wherein the therapeutically effective amount is from about 10 mg/ml to about 100 mg/ml.

35     35. The pharmaceutical composition of claim 28, wherein the carrier is a gel and the pharmaceutical composition is a suppository.

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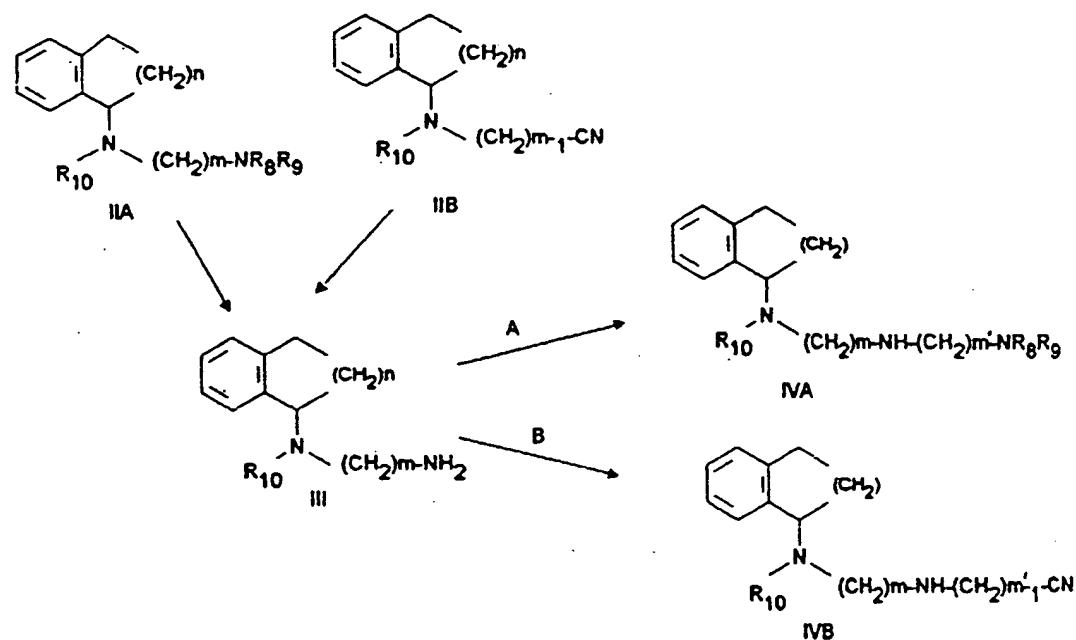
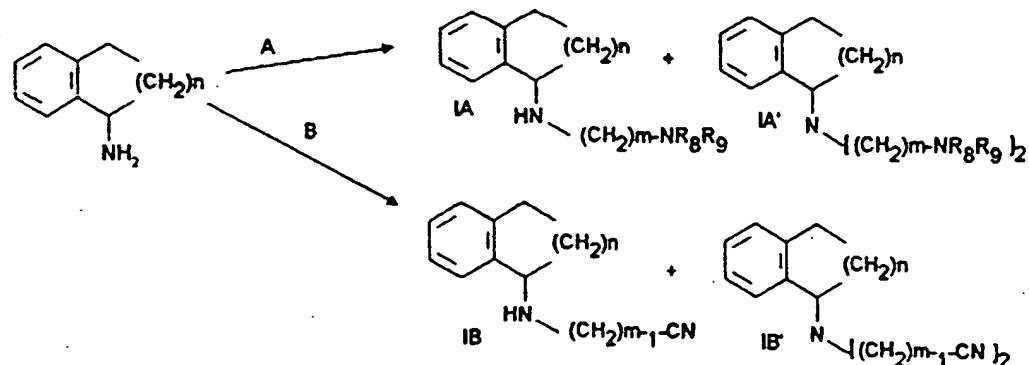
36. A method of treating acute neurological traumatic disorder or neurotrauma in a subject comprising administering to the subject a therapeutically effective amount of the compound of claim 1 or pharmaceutically acceptable salt thereof, effective to treat the acute neurological traumatic disorder or neurotrauma in the subject.  
5
37. A method of treating a subject afflicted with a neurodegenerative disease which comprises administering to the subject an amount of the compound of claim 1 or pharmaceutically acceptable salt thereof, effective to treat the neurodegenerative disease in the subject.  
10
38. A method of treating a subject afflicted with a neurotoxic injury which comprises administering to the subject an amount of the compound of claim 1 or pharmaceutically acceptable salt thereof, effective to treat the neurotoxic injury in the subject.  
15
39. A method of treating a subject afflicted with brain ischemia which comprises administering to the subject an amount of the compound of claim 1 or pharmaceutically acceptable salt thereof, effective to treat brain ischemia in the subject.  
20
40. A method of treating a subject afflicted with a head trauma injury which comprises administering to the subject an amount of the compound of claim 1 or pharmaceutically acceptable salt thereof, effective to treat the head trauma injury in the subject.  
25
41. A method of treating a subject afflicted with a spinal trauma injury which comprises administering to the subject an amount of the compound of claim 1 or pharmaceutically acceptable salt thereof,  
30
- 35

-63-

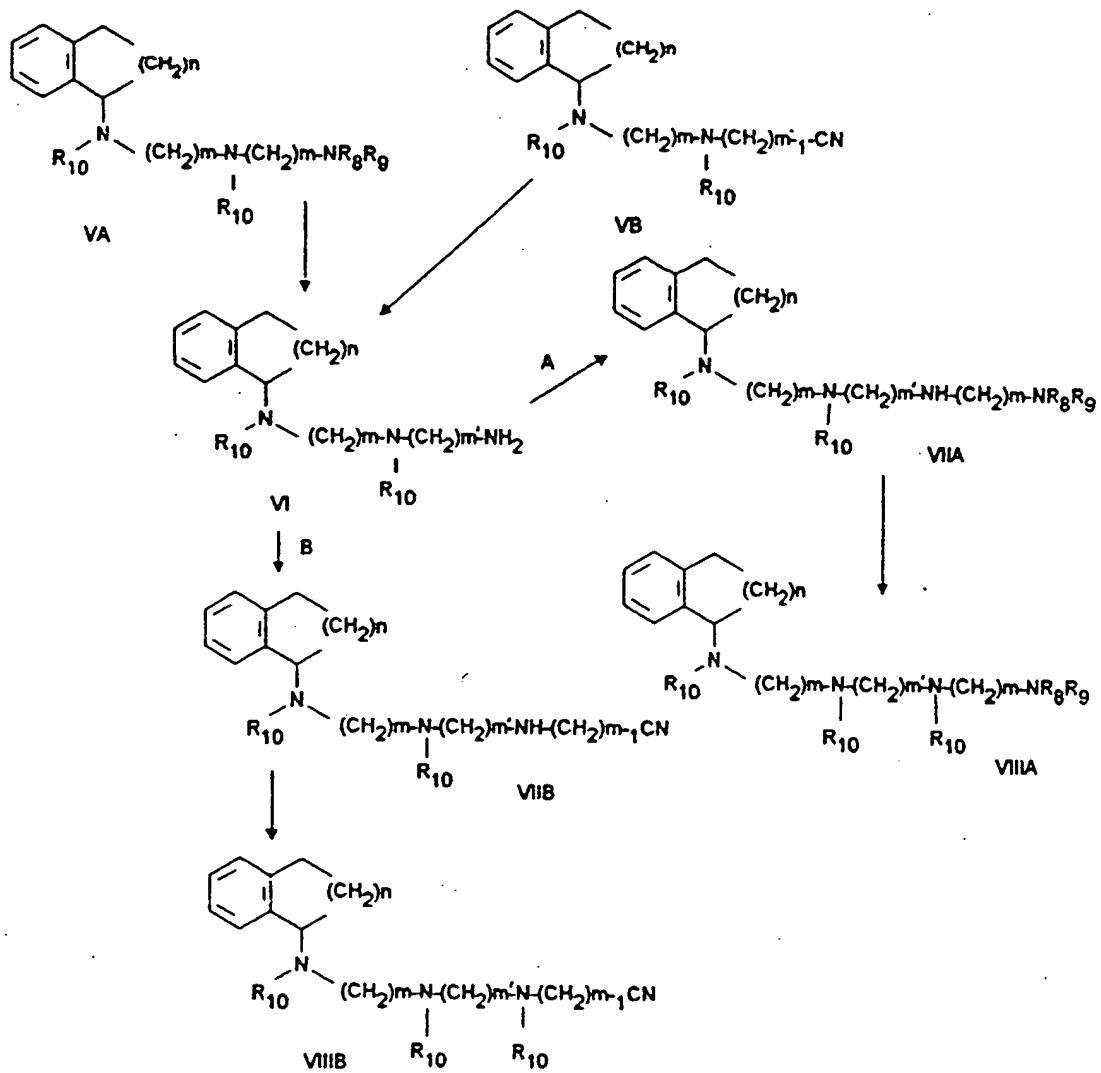
effective to treat the spinal trauma injury in the subject.

42. A method of preventing nerve damage in a subject  
5 which comprises administering to the subject an amount of the compound of claim 1 or pharmaceutically acceptable salt thereof, effective to prevent nerve damage in the subject.

1/5

**FIGURE 1A****Scheme I**

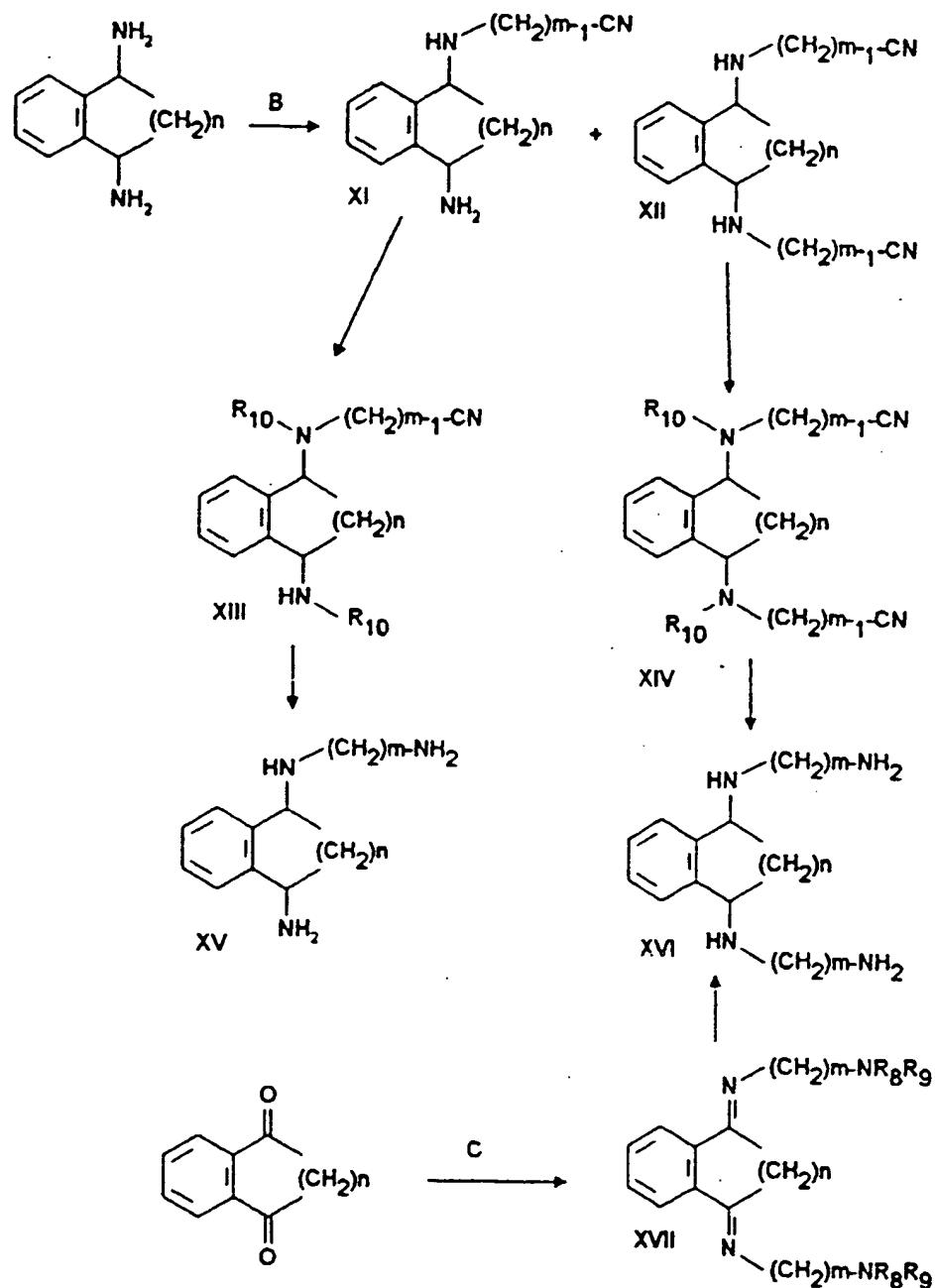
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**FIGURE 1B****Scheme I cont.**

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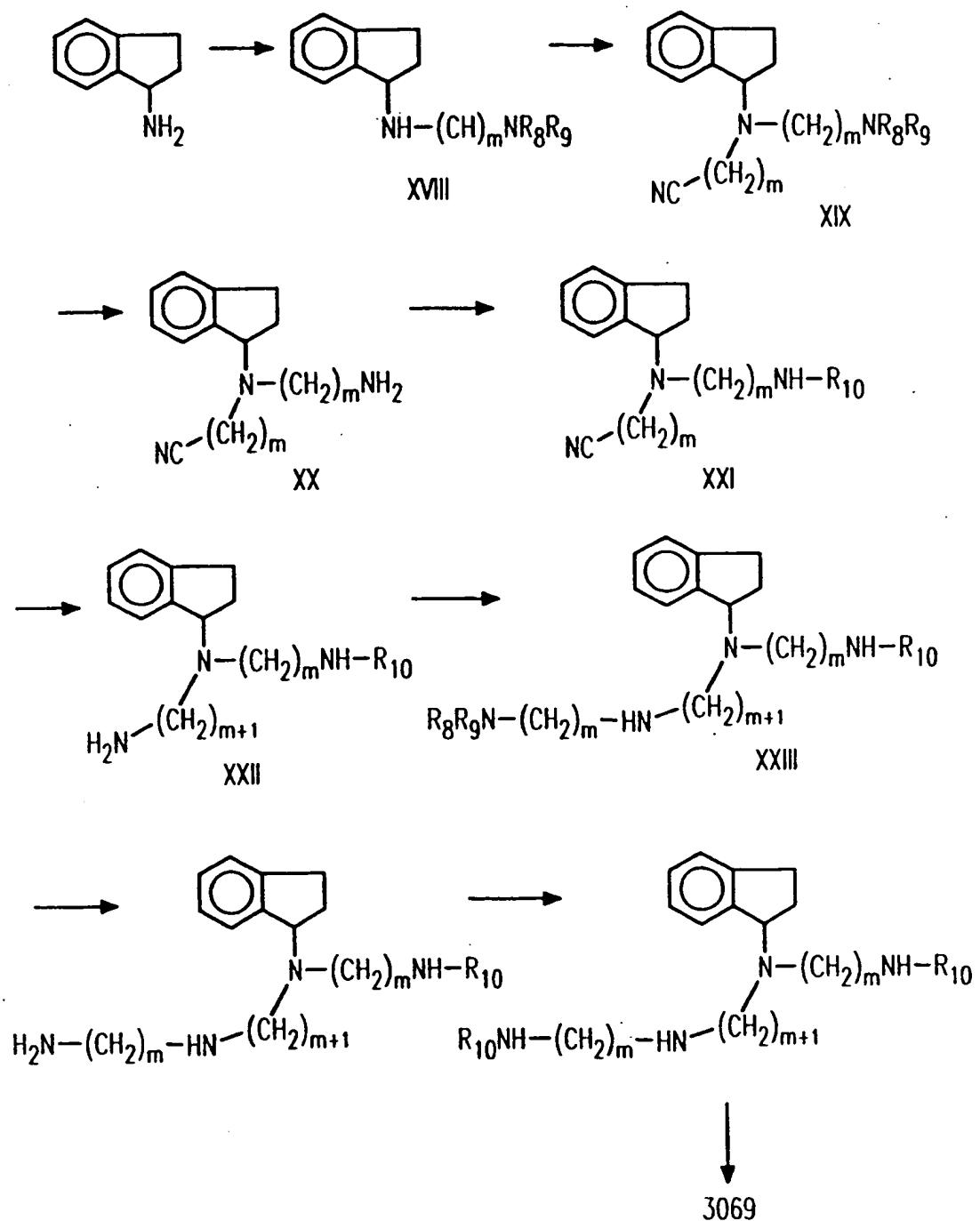
FIGURE 2

Scheme II



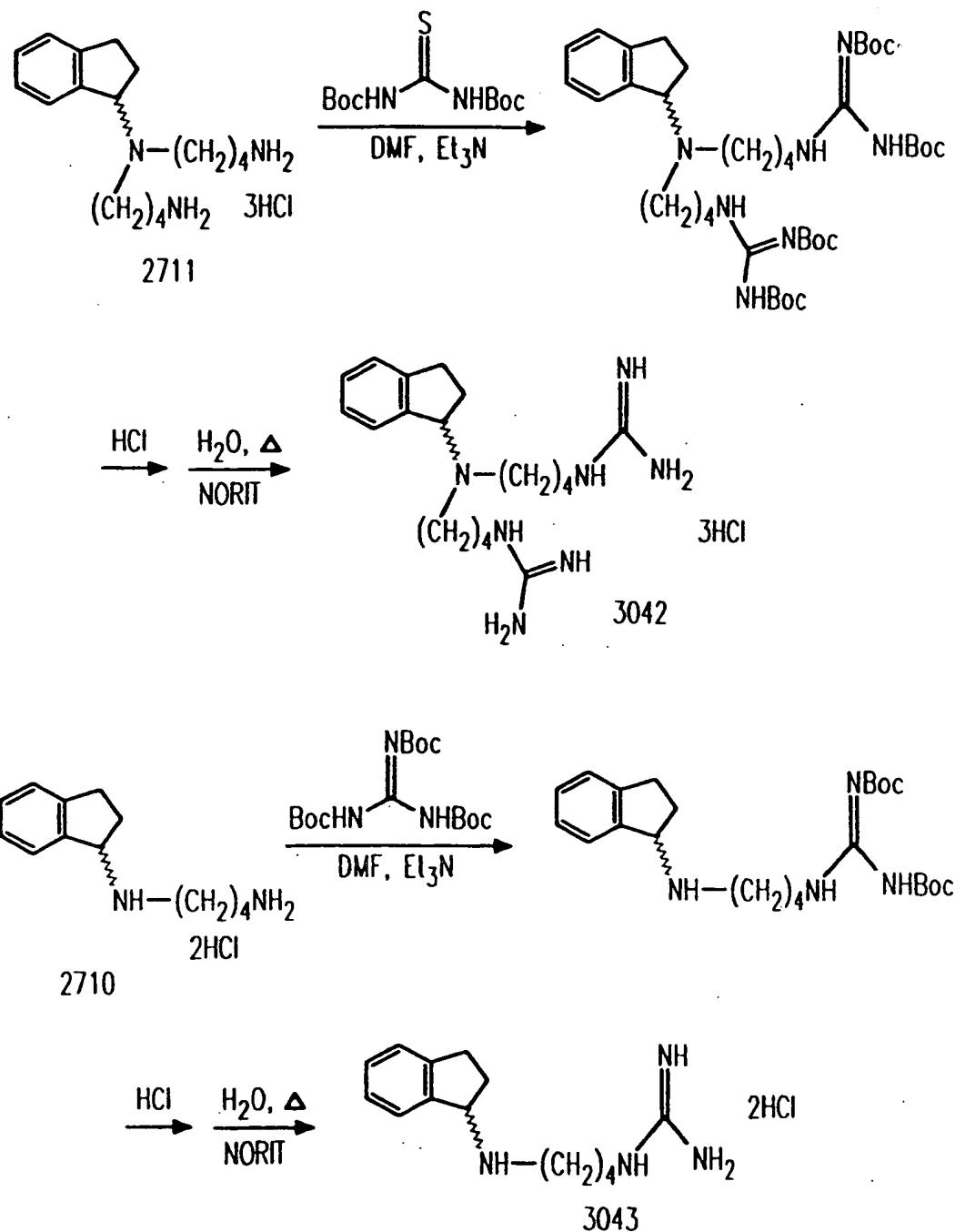
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FIGURE 3



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FIGURE 4



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/11318

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/15, 31/155; C07C 243/20, 247/14, 279/12, 281/16.

US CL : 514/616, 632, 634, 657; 564/222, 228, 236, 238, 428.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/616, 632, 634, 657; 564/222, 228, 236, 238, 428.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE - structure search.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,953,506 A (SPICER ET AL.) 27 April 1976 (27.04.76), column 27, lines 30-35.	1-3, 17, 19, 20, 23-26, 28-35
X	US 4,792,628 A (OSHIRO ET AL.) 20 December 1988 (20.12.88), column 30, example 20.	1-3, 17, 19, 20, 23-26, 28-35
X	HUEBNER et al. A Product of the Chemical Reduction of o-Benzenediacetonitrile. Journal of Organic Chemistry. December 1962, Vol. 27, pages 4465-4469, especially compounds VIII and IXa and the examples on pages 4468 and 4469.	1-5, 7, 23-26

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
• "A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
• "E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
• "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
• "O" document referring to an oral disclosure, use, exhibition or other means		
• "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

02 AUGUST 1996

Date of mailing of the international search report

21 AUG 1996

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